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7 Treatments for Mood Disorders: So-Called “Antidepressants” and “Mood Stabilizers”

Treatments for Mood Disorders: So-Called “Antidepressants” and “Mood Stabilizers” Definitions of Clinical Effects of Treatment in Depression 284 How Well Do Classic Monoamine Reuptake Blockers Work in Unipolar Depression? 285 Redefining “Mood Stabilizers”: A Labile Label 288 Drugs for Unipolar Depression 289 Selective Serotonin Reuptake Inhibitors (SSRIs) 289 Serotonin Partial Agonist Reuptake Inhibitors (SPARIs) 296 Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) 298 Norepinephrine–Dopamine Reuptake Inhibitors (NDRIs): Bupropion 303 Agomelatine 306 Mirtazapine 308 Serotonin Antagonist/Reuptake Inhibitors (SARIs) 311 Vortioxetine 315 Neuroactive Steroids 320 Treatment Resistance in Unipolar Depression 323 Choosing Treatment for Treatment Resistance in Depression on the Basis of Genetic Testing 323 Augmenting Strategies for Unipolar Depression 325 Second-Line Monotherapies Used for TreatmentResistant Depression 333 Drugs for Bipolar Disorder Spectrum 338 Serotonin/Dopamine Blockers: Not Just for Psychosis and Psychotic Mania 338 Lithium, the Classic “Antimanic” and “Mood Stabilizer” 345 Anticonvulsants as “Mood Stabilizers” 346 Anticonvulsants with Proven Efficacy in Bipolar Disorder 347 Combinations are the Standard for Treating Bipolar Disorder 353 Future Treatments for Mood Disorders 353 Dextromethorphan–Bupropion and Dextromethorphan–Quinidine 353 Dextromethadone 355 Hallucinogen-Assisted Psychotherapy 355 Summary 358 In this chapter, we will review pharmacological concepts underlying the use of drugs used to treat mood disorders, from depression, to mixed states, to mania. These agents have classically been called “antidepressants” and “mood stabilizers” but this terminology is now considered out of date and confusing since not all drugs classically called “antidepressants” are used to treat all forms of depression – especially not bipolar depression or depression with mixed features. Furthermore, many of the classic so-called “antidepressants” are also used to treat a whole range of disorders from anxiety disorders,

to eating disorders, traumatic disorders, obsessive compulsive and impulsive disorders, pain, and beyond. Finally, many of the drugs used for psychosis and discussed extensively in Chapter 5 are used even more commonly to treat depression, unipolar, bipolar, and mixed depression, as well as mania, yet are not generally classed as “antidepressants” although they are certainly “drugs for depression.” To eliminate confusion about how to discuss categories of drugs, throughout this textbook we strive to utilize modern neuroscience-based nomenclature, where drugs are named for their pharmacological mechanism of action and not for their clinical indication. Thus, drugs discussed in this chapter have “antidepressant action” but are not called “antidepressants.” Other drugs have mood-stabilizing and antimanic action but are not called “mood stabilizers.” What is a “mood stabilizer”? Originally, a mood stabilizer was a drug that treated mania and prevented recurrence of mania, thus “stabilizing” the manic pole of bipolar disorder. Others use this term for a drug that treats depression and recurrence of depression in bipolar disorder thus stabilizing the depressed pole of bipolar disorder. Rather than use the term for stabilizing either mania or depression, here we will use terms to describe

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY and categorize agents that treat bipolar disorder based upon presumed mechanism of therapeutic action. This chapter will review some of the most extensively prescribed psychotropic agents in psychiatry today, namely those that target neurotransmitter transporters, receptors, and ion channels. The goal of this chapter is to acquaint the reader with current and evolving ideas about how the various drugs used to treat disorders of mood work. We will explain the mechanisms of action of these drugs by building upon general pharmacological concepts introduced in earlier chapters. We will also discuss concepts about how to use these drugs in clinical practice, including strategies for what to do if initial treatments fail and how to rationally combine one drug with another. Finally, we will introduce the reader to several new agents targeting mood disorders, which have recently been approved or are in clinical development. Our discussion of drugs for the treatment of mood disorders in this chapter is at the conceptual level, and not at the pragmatic level. The reader should consult standard drug handbooks (such as the companion Stahl’s Essential Psychopharmacology: the Prescriber’s Guide) for details of doses, side effects, drug interactions, and other issues relevant to the prescribing of these drugs in clinical practice. Here we will discuss putting together a “portfolio” of two or more mechanisms of action, often requiring more than one drug, as a strategy for patients who have not responded to single pharmacological mechanisms. This treatment strategy for mood disorders is very different than that for schizophrenia, discussed in Chapter 5, where single antipsychotic drugs as treatments are the rule and the expected improvement in MIXED FEATURES OF MANIA response MIXED FEATURES OF DEPRESSION response 50% medication treatment symptomatology may be only 20% to 30% reduction of symptoms, with few, if any, patients with schizophrenia becoming truly asymptomatic. By contrast, in mood disorders there is a greater chance to reach a genuine state of sustained and asymptomatic remission and the challenge for those who treat these patients is to help them attain this best outcome whenever possible. That is the reason for learning the mechanisms of action of so many drugs, the complex biological rationale for combining specific sets of drugs, and the practical tactics for tailoring a unique drug treatment portfolio to fit the needs of an individual patient. DEFINITIONS OF CLINICAL EFFECTS OF TREATMENT IN DEPRESSION For patients who have a major depressive episode, unipolar, bipolar, or mixed, and who receive treatment and improve to the level 50% reduction of symptoms or more, this outcome is called a response (Figure 7-1). This used to be the goal of treatment with drugs for depression: namely, reduce symptoms substantially, and by at least 50%. However, the paradigm for depression

treatment has shifted dramatically in recent years so that now the goal is complete remission of symptoms (Figure 7-2), and maintaining that level of improvement so that the patient's major depressive episode does not relapse shortly after remission, nor does the patient have a recurrent episode in the future (Figure 7-3). Given the known limits to the efficacy of available drugs to treat depression, especially when multiple treatment options Figure 7-1 Response in depression. When treatment of a major depressive episode results in at least 50% improvement in symptoms, it is called a response. Such patients are better but not well. Previously, this was considered the goal of depression treatment. HYPOMANIA

HYPOMANIA remission recovery MIXED FEATURES OF MANIA 100% MIXED FEATURES OF DEPRESSION acute 6-12 weeks medication treatment maintenance 1 or more years continuation 4-9 months time relapse recurrence MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION acute 6-12 weeks medication treatment continuation 4-9 months maintenance 1 or more years time are not deployed aggressively and early in the course of this illness, the goal of sustained remission can be difficult to reach. Unfortunately, remission is usually not reached with the first agent chosen to treat depression. HOW WELL DO CLASSIC MONOAMINE REUPTAKE BLOCKERS WORK IN UNIPOLAR DEPRESSION? The mechanism of action of drugs for unipolar depression is predominantly inhibition of monoamine reuptake as explained in detail in the following several sections. Before tackling the mechanism, we can ask, how well do they work? Real-world trials suggest that only a Chapter 7: Treatments for Mood Disorders Figure 7-2 Remission in depression. When treatment of major depressive episode results in removal of essentially all symptoms, it is called remission for the first several months and then recovery if it is sustained for longer than several months. Such patients are not just better – they are well. However, they are not cured, since depression can still recur. Remission and recovery are now the goals when treating patients with depression. Figure 7-3 Relapse and recurrence in depression. When depression returns before there is a full remission of symptoms or within the first several months following remission of symptoms, it is called a relapse. When depression returns after a patient has recovered, it is called a recurrence. HYPOMANIA third of patients with unipolar depression remit on their first treatment with a drug from this class, and even after about a year of total treatment with a sequence of four different drugs for unipolar depression, each given for 12 weeks, only about two-thirds of patients with unipolar depression ever achieve remission of their symptoms (Figure 7-4). If patients do not fully remit after treatment, what are the most common symptoms that persist? The answer is shown in Figure 7-5, and the symptoms include insomnia, fatigue, multiple painful physical complaints (even though these are not part of the formal diagnostic criteria for depression), cognitive problems including difficulty concentrating, and lack of interest or motivation. Drugs for unipolar depression often appear 285

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY What Proportion of Unipolar Major Depressive Episodes Remit? HYPOMANIA MIXED FEATURES OF MANIA 33% 20% 6-7% 6-7% MIXED FEATURES OF DEPRESSION 67% 40% 47% treatment #1 treatment #2 treatment #3 treatment #4 3 months 3 months 3 months What Are the Most Common Residual Symptoms in Nonremitters? MIXED FEATURES OF MANIA complete remission 33% residual symptoms 67% least common MIXED FEATURES OF DEPRESSION most common treatment to work better in improving depressed mood, suicidal ideation, and psychomotor retardation (Figure 7-5). Why should we care whether a patient is in remission from major depression or has just a few persistent symptoms? Part of the answer can be found in Chapter 6 in the discussion of neuroprogression from persisting symptoms to loss

of synapses, loss of neurons, and treatment resistance (Figures 6-11, 6-28 through 6-33). The other part of the answer can be found in Figure 7-6, which illustrates the evolution of treatment resistance over time, mostly because symptoms persist or return. On the one hand, Figure 7-6 shows that if a drug for unipolar depression gets your patient into remission, that patient has a significantly lower relapse rate than if no treatment Figure 7-4 Remission rates in unipolar depression. Approximately one-third of patients with unipolar depression will remit during treatment with any treatment initially. Unfortunately, for those who fail to remit, the likelihood of remission with another monotherapy goes down with each successive trial. Thus, after a year of treatment with four sequential monotherapies taken for 12 weeks each, only two-thirds of patients will have achieved remission. 67% remission after 4 treatments 33% nonremitters after 4 treatments Figure 7-5 Common residual symptoms. In patients who do not achieve remission, the most common residual symptoms are insomnia, fatigue, painful physical complaints, problems concentrating, and lack of interest. The least common residual symptoms are depressed mood, suicidal ideation, and psychomotor retardation. HYPOMANIA depressed mood suicidal ideation psychomotor retardation insomnia fatigue/pain concentration/ interest was given at all. On the other hand, the bad news is that there are still very frequent relapses in the remitters, and these relapse rates are more frequent and come quicker the more treatments the patient needs in order to get into remission (Figure 7-6). Data like these have galvanized researchers and clinicians alike to treat patients to the point of remission of all symptoms whenever possible, and to try to intervene as early as possible in this illness of unipolar major depression, not only to be merciful in trying to relieve current suffering from all depressive symptoms, but also because of the possibility that aggressive treatment may prevent disease progression (see Chapter 6 and Figures 6-11, 6-28 through 6-33). The concept of disease progression in

Chapter 7: Treatments for Mood Disorders Figure 7-6 Relapse rates. The rate of relapse of major depression is significantly less for patients who achieve remission. However, there is still a risk of relapse even in remitters, and the likelihood increases with the number of treatments it takes to get the patient to remit. Thus, the relapse rate for patients who do not remit ranges from 60% at 12 months after one treatment to 70% at 6 months after four treatments. For those who do remit, the relapse rate ranges from only 33% at 12 months after one treatment all the way to 70% at 6 months after four treatments. In other words, the protective nature of remission virtually disappears once it takes four treatments to achieve remission. What Proportion of Unipolar Major Depressive Episodes Relapse? after 1 treatment after 2 treatments relapse rate 100% 0% 33% in remission not in remission 60% months months months relapse rate 100% 0% 50% in remission not in remission 67% months months months after 3 treatments after 4 treatments relapse rate 100% 0% 50% 50% in remission not in remission 70% 70% months months months relapse rate 100% 0% 30% in remission not in remission months months months

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY mood disorders is unproven and provocative, but makes a good deal of sense intuitively to many clinicians and investigators. The idea is that chronicity of a mood disorder, relapses of a mood disorder, and development of treatment resistance could all be reduced, with a better overall outcome in patients with aggressive treatment that leads to remission of all symptoms, thus potentially modifiying the course of this illness. REDEFINING “MOOD STABILIZERS”: A LABILE LABEL “There is no such thing as a mood stabilizer.” – US FDA What Is a “Mood Stabilizer”: Mania-Minded Treatments treat from above HYPOMANIA stabilize from above MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION

What Is a “Mood Stabilizer”: Depression-Minded Treatments HYPOMANIA MIXED FEATURES OF MANIA MIXED FEATURES OF DEPRESSION stabilize from below treat from below “Long live the mood stabilizers.” – Prescribers What is a “mood stabilizer?” As mentioned above, originally, a mood stabilizer was a drug that treated mania and prevented recurrence of mania, thus “stabilizing” the manic pole of bipolar disorder. More recently, the concept of mood stabilizer has been defined in a wide-ranging manner, from “something that acts like lithium,” to “an anticonvulsant used to treat bipolar disorder,” to “an antipsychotic used to treat bipolar disorder,” to “stabilizing both mania and depression in bipolar disorder.” Rather than using the term mood stabilizers, regulatory authorities consider that there are drugs that can treat any or all of four distinct phases Figure 7-7 Mania-minded treatments. Although the ideal “mood stabilizer” would treat both mania and bipolar depression while also preventing episodes of either pole, in reality different agents may be efficacious for different phases of bipolar disorder. Some agents may be “mania-minded” and thus able to “treat from above” and/or “stabilize from above” – in other words, to reduce and/ or prevent symptoms of mania. Figure 7-8 Depression-minded treatments. Although the ideal “mood stabilizer” would treat both mania and bipolar depression while also preventing episodes of either pole, in reality different agents may be efficacious for different phases of bipolar disorder. Some agents may be “depression-minded” and thus able to “treat from below” and/or “stabilize from below” – in other words, to reduce and/or prevent symptoms of bipolar depression.

of the illness (Figures 7-7 and 7-8). Thus, a drug can be “mania-minded” and “treat from above” to reduce symptoms of mania, and/or “stabilize from above” to prevent relapse and recurrence of mania (Figure 7-7). Furthermore, drugs can be “depression-minded” and “treat from below” to reduce symptoms of bipolar depression, and/or “stabilize from below” to prevent relapse and recurrence of depression (Figure 7-8). Not all drugs proven to work in bipolar disorder have all four therapeutic actions. In this chapter, we will discuss agents that have one or more of these actions in bipolar disorder, but will not refer to any of these agents as “mood stabilizers” but instead to their presumed pharmacological mechanism of action. DRUGS FOR UNIPOLAR DEPRESSION Selective Serotonin Reuptake Inhibitors (SSRIs) Rarely has a class of drugs transformed a field as dramatically as the SSRIs have transformed clinical psychopharmacology. Some estimate that SSRI prescriptions in the US alone occur at the rate of 7 prescriptions per second: over 225 million a year. Clinical indications for use of SSRIs range far beyond unipolar major depressive disorder, to a number of anxiety disorders, posttraumatic stress disorder (PTSD), obsessive–compulsive disorder (OCD), and also to premenstrual dysphoric disorder, eating disorders, and SSRI SERT Figure 7-9 Selective serotonin reuptake inhibitors. Shown here is an icon depicting the core feature of selective serotonin reuptake inhibitors (SSRIs), namely serotonin reuptake inhibition. Although the agents in this class have unique pharmacological profiles, they all share the common property of serotonin transporter (SERT) inhibition. Chapter 7: Treatments for Mood Disorders others. There are six principal agents in this group, described below, and all share the common property of serotonin reuptake inhibition; thus, they all belong to the same drug class, known as SSRIs. However, each of these six drugs also has additional unique pharmacological properties that allow them to be distinguished from each other. First, we will discuss what these six drugs share in common, and then we will explore their distinctive individual properties that allow sophisticated prescribers to match specific drug profiles to individual patient symptom profiles. What the Six SSRIs Have in Common All the six SSRIs have the same major pharmacological feature in common: selective and potent inhibition of serotonin reuptake, also known as inhibition of the serotonin transporter

(SERT). This simple concept is shown in Figures 7-9 and 7-10. Although the action of SSRIs at the presynaptic axon terminal has classically been emphasized (Figure 7-10), it now appears that events occurring at the somatodendritic end of the serotonin neuron (near the cell body) may be more important in explaining the therapeutic actions of the SSRIs (Figures 7-11 through 7-15). That is, in the SSRI Action Figure 7-10 SSRI action. The serotonin reuptake inhibitor (SRI) portion of the SSRI molecule is shown inserted into the serotonin reuptake pump (the serotonin transporter, or SERT), blocking it, and causing increased synaptic availability of serotonin. 289

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A Depressed state: low 5HT, upregulated receptors, low number of signals in the neuron to release more 5HT 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A Antidepressant action: SSRI blocks 5HT reuptake both at the dendrites and at the axon depressed state, the monoamine hypothesis of depression states that serotonin may be deficient, both at presynaptic somatodendritic areas near the cell body (Figure 7-11, left) and in the synapse itself, near the axon terminal (Figure 7-11, right). The neurotransmitter receptor hypothesis proposes that monoamine receptors may be upregulated, as shown in Figure 7-11, representing the depressed state before treatment. Neuronal firing rates Figure 7-11 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 1. According to the monoamine hypothesis of depression, there is a relative deficiency of serotonin (5HT) (see levels of 5HT both in the synapse near the axon terminal [right] and at somatodendritic areas [left]. According to the neurotransmitter receptor hypothesis of depression, the number of 5HT receptors is upregulated, including presynaptic 5HT1A autoreceptors as well as postsynaptic 5HT receptors. 5HT1A autoreceptor 1A 5HT postsynaptic receptor SERT E Figure 7-12 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 2. When an SSRI is administered, it immediately blocks the serotonin reuptake pump or transporter (SERT) (see icon of an SSRI blocking SERT). However, this causes serotonin (5HT) to increase initially only in the somatodendritic area of the 5HT neuron (left) and not very much in the areas of the brain where the axons terminate (right). When 5HT levels rise in the somatodendritic area, this stimulates nearby 5HT1A autoreceptors. 5HT1A autoreceptor 1A 5HT postsynaptic receptor SERT SSRI E for this neuron may also be dysregulated in depression, contributing to regional abnormalities in information processing, and the development of specific symptoms, depending upon the region affected, as discussed in Chapter 6 and shown in Figure 6-38. When an SSRI is given acutely, it is well known that serotonin (5HT) rises due to blockade of SERT. What is somewhat surprising, however, is that blocking the

1A 1A 1A 1A 1A The increase in 5HT causes the autoreceptors to desensitize/downregulate presynaptic SERT does not immediately lead to a great deal of serotonin in many synapses. In fact, when SSRI treatment is initiated, 5HT rises immediately at the somatodendritic area located in the midbrain raphe (Figure 7-12, left) due to blockade of SERTs there, rather than in the areas of the brain where the axons terminate (Figure 7-12, right). The somatodendritic area of the serotonin neuron is therefore where 5HT increases first (Figure 7-12, left). Serotonin receptors in this brain area have 5HT1A pharmacology, as discussed in Chapter 4 and illustrated in Figure 4-39. When serotonin levels rise in the somatodendritic area, this stimulates nearby 5HT1A autoreceptors (also on the left in Figure 7-12). These immediate pharmacological actions obviously cannot explain the delayed therapeutic actions of the SSRIs. However, these immediate actions may explain the immediate side effects that are caused by the SSRIs when treatment is initiated. Over time, the increased 5HT levels acting at the somatodendritic 5HT1A autoreceptors causes them to

downregulate and become desensitized (Figure 7-13, left). This desensitization occurs because the increase in serotonin is recognized by these presynaptic 5HT1A receptors, and this information is sent to the cell nucleus of the serotonin neuron. The genome's reaction to this information is to issue instructions that cause these same receptors to become desensitized over time. The time course of this desensitization correlates with the onset of therapeutic actions of the SSRIs (Figure 6-25). Chapter 7: Treatments for Mood Disorders Figure 7-13 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 3. The consequence of increased serotonergic binding at somatodendritic 5HT1A autoreceptors is that they desensitize or downregulate (red circle, compare to Figure 7-12). E Once the 5HT1A somatodendritic autoreceptors are desensitized, 5HT can no longer effectively turn off its own release. Since 5HT is no longer inhibiting its own release, the serotonin neuron is therefore disinhibited (Figure 7-14). This results in a flurry of 5HT release from axons and an increase in neuronal impulse flow (shown as lightning in Figure 7-14 and release of serotonin from the axon terminal on the right). This is just another way of saying the serotonin release is "turned on" at the axon terminals. The serotonin that now pours out of the various projections of serotonin pathways in the brain is what theoretically mediates the various therapeutic actions of the SSRIs. While the presynaptic somatodendritic 5HT1A autoreceptors are desensitizing (Figure 7-13), 5HT is building up in synapses (Figure 7-14), and causes the postsynaptic 5HT receptors to desensitize as well (Figure 7-15, right). These various postsynaptic 5HT receptors in turn send information to the cell nucleus of the postsynaptic neuron that serotonin is targeting (on the far right of Figure 7-15). The reaction of the genome in the postsynaptic neuron is also to issue instructions to downregulate or desensitize some of these receptors as well. The time course of this desensitization correlates with the onset of tolerance to the side effects of the SSRIs (Figure 7-15). This theory thus suggests a pharmacological cascading mechanism whereby the SSRIs exert their therapeutic actions: namely, powerful but delayed disinhibition of serotonin release in key pathways throughout the brain. Furthermore, side effects are hypothetically caused by the acute actions of serotonin at undesirable receptors in 291

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY 1A 1A 1A 1A 1A The downregulation of the autoreceptors causes the neuron to release more 5HT at the axon 1A 1A 1A 1A 1A The increase of 5HT at the axon causes the postsynaptic receptors to desensitize/downregulate, reducing side effects undesirable pathways. Finally, side effects may attenuate over time by desensitization of the very receptors that mediate them. Unique Properties of Each SSRI: The Not-So-Selective Serotonin Reuptake Inhibitors Although the six SSRIs clearly share the same mechanism of action, individual patients often react very differently Figure 7-14 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 4. Once the somatodendritic 5HT1A receptors downregulate, there is no longer inhibition of impulse flow in the serotonin (5HT) neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of 5HT in the axon terminal (red circle). This increase is delayed compared with the increase of 5HT in the somatodendritic areas of the 5HT neuron; the delay is the result of the time it takes for somatodendritic 5HT to downregulate the 5HT1A autoreceptors and turn on neuronal impulse flow in the 5HT neuron. This delay may explain why SSRIs do not relieve depression immediately. It is also the reason why the mechanism of action of SSRIs may be linked to increasing neuronal impulse flow in 5HT neurons, with 5HT levels increasing at axon terminals before an SSRI can exert its therapeutic effects. E Figure 7-15 Mechanism of action of selective serotonin reuptake inhibitors (SSRIs), part 5. Finally, once the SSRIs have blocked the reuptake pump (or serotonin transporter [SERT]), increased somatodendritic serotonin (5HT), desensitized somatodendritic 5HT1A autoreceptors, turned on

neuronal impulse flow, and increased release of 5HT from axon terminals, the final step may be the desensitization of postsynaptic 5HT receptors (red circle). This desensitization may mediate the reduction of side effects of SSRIs as tolerance develops. E to one SSRI versus another. This is not generally observed in large clinical trials where mean group differences between two SSRIs either in efficacy or side effects are very difficult to document. Rather, such differences are seen by prescribers treating patients one at a time, with some patients experiencing a therapeutic response to one SSRI and not another, and other patients tolerating one SSRI and not another.

If blockade of SERT explains the shared clinical and pharmacological actions of SSRIs, what explains their differences? Although there is no generally accepted explanation that accounts for the commonly observed clinical phenomena of different efficacy and tolerability of various SSRIs in individual patients, it makes sense to consider those unique pharmacological characteristics of the six SSRIs that are not shared with each other as candidates to explain the broad range of individual patient reactions to different SSRIs (Figures 7-16 through 7-21). Each SSRI has secondary pharmacological actions other than SERT blockade, and no two SSRIs have identical secondary pharmacological characteristics. Whether these secondary binding profiles can account for the differences in efficacy and tolerability in individual patients remains to be proven. However, it does lead to provocative hypothesis generation and gives a rational basis for psychopharmacologists trying more than one of these agents rather than thinking “they are all the same.” Sometimes only an empiric trial of different SSRIs will lead to the best match of drug to an individual patient. Fluoxetine: An SSRI with 5HT2C Antagonist Properties In addition to serotonin reuptake inhibition, fluoxetine also has 5HT2C antagonist actions that may explain many of its unique clinical properties (Figure 7-16). 5HT2C antagonism may contribute to its antidepressant actions and also to its efficacy in other disorders, especially in eating disorders. Other drugs for unipolar fluoxetine NET 5HT2C SERT SERT Figure 7-16 Fluoxetine. In addition to serotonin reuptake inhibition, fluoxetine has norepinephrine reuptake inhibition (NRI) and serotonin 2C antagonist actions (5HT2C). 5HT2C antagonism can lead to disinhibition of norepinephrine and dopamine; this action may be responsible for fluoxetine’s activating effects. NRI may be clinically relevant only at very high doses. Chapter 7: Treatments for Mood Disorders depression with 5HT2C antagonist properties include trazodone, mirtazapine, agomelatine, and some tricyclic antidepressants, and these will be described below. Finally, two serotonin 2A/dopamine 2 antagonists, quetiapine (Figure 5-45) and olanzapine (Figure 5-44), also have potent 5HT2C antagonist properties. Both agents are used to treat psychosis (see Chapter 5) but are also approved for augmenting other drugs for unipolar depression, treatment-resistant unipolar depression, and bipolar depression. Blocking serotonin action at 5HT2C receptors disinhibits (i.e., enhances) release of both norepinephrine and dopamine, actions theoretically beneficial for the treatment of depression (see Chapter 6 and Figure 6-24B and also the discussion below on agomelatine). The good news about 5HT2C antagonism may be that it is generally activating, and the reason why many patients, even from the first dose, detect an energizing and fatigue-reducing effect of fluoxetine, with improvement in concentration and attention as well. This mechanism is perhaps best matched to depressed patients with reduced positive affect (Figure 6-41), hypersomnia, psychomotor retardation, apathy, and fatigue. Fluoxetine is also approved in some countries in combination with olanzapine for treatment-resistant unipolar depression and for bipolar depression. Since olanzapine also has 5HT2C antagonist actions (Figure 5-44), it may be that adding the 5HT2C antagonist actions of olanzapine to those of fluoxetine could theoretically lead to further enhanced dopamine and norepinephrine release in the cortex to mediate the antidepressant actions of this combination.

5HT2C antagonism may also contribute to the anti-bulimia effect of higher doses of fluoxetine, the only SSRI approved for the treatment of this eating disorder. The bad news could be that 5HT2C antagonist actions of fluoxetine may contribute to this agent being sometimes less well matched to patients with agitation, insomnia, and anxiety, who may experience unwanted activation and even a panic attack if given an agent that further activates them. Fluoxetine also has weak norepinephrine reuptake blocking properties (Figure 7-16), which may become clinically relevant at very high doses. Fluoxetine has a long half-life (2–3 days), and its active metabolite an even longer half-life (2 weeks). The long halflife is advantageous in that it seems to reduce the withdrawal reactions that are characteristic of sudden discontinuation of some SSRIs, but it also means that it takes a long time to clear the drug and its active 293

 metabolite after discontinuing fluoxetine, and prior to starting other agents such as a monoamine oxidase (MAO) inhibitor. Fluoxetine is not only available as a once-daily formulation, but also as a once-weekly oral dosage formulation. Sertraline: An SSRI with Dopamine Transporter (DAT) Inhibition and σ1 Binding This SSRI has two candidate mechanisms that distinguish it: dopamine transporter (DAT) inhibition and σ1 receptor binding (Figure 7-17). The DAT inhibitory actions are controversial since they are weaker than the SERT inhibitory actions, thus leading some experts to suggest that there is not sufficient DAT occupancy by sertraline to be clinically relevant. However, as will be discussed later in the section on norepinephrine–dopamine reuptake inhibitors (NDRIs), it is not clear that high degrees of DAT occupancy are necessary or even desirable in order to contribute to antidepressant actions. That is, perhaps only a small amount of DAT inhibition is sufficient to cause improvement in energy, motivation, and concentration, especially when added to another action such as SERT inhibition. In fact, high-impact DAT inhibition is the property of reinforcing stimulants, including cocaine and methamphetamine, and would not generally be desired in a drug for depression (see discussion of DAT inhibitors in Chapter 11 on ADHD and Chapter 13 on impulsivity, compulsivity, and addiction). sertraline DAT SERT SERT Figure 7-17 Sertraline. Sertraline has dopamine transporter (DAT) inhibition and σ1 receptor binding in addition to serotonin reuptake inhibition (SRI). The clinical relevance of sertraline's DAT inhibition is unknown, although it may improve energy, motivation, and concentration. Its sigma properties may contribute to anxiolytic actions and may also be helpful in patients with psychotic depression. Anecdotally, clinicians have observed the mild and desirable activating actions of sertraline in some patients with "atypical depression," improving symptoms of hypersomnia, low energy, and mood reactivity. A favorite combination of some clinicians for depressed patients is to add bupropion to sertraline (i.e., Wellbutrin to Zoloft, sometimes called "Well-oft"), adding together the weak DAT inhibitory properties of each agent. Clinicians have also observed the overactivation of some patients with panic disorder by sertraline, thus requiring slower dose titration in some patients with anxiety symptoms. All of these actions of sertraline are consistent with weak DAT inhibitory actions contributing to its clinical portfolio of actions. The σ1 actions of sertraline are not well understood, but might contribute to its anxiolytic effects and especially to its effects in psychotic and delusional depression, where sertraline may have advantageous therapeutic effects compared to some other SSRIs. Paroxetine: An SSRI with Muscarinic Anticholinergic and Norepinephrine Transporter (NET) Inhibitory Actions This SSRI tends to be more calming, even sedating, early in treatment compared to the more activating actions of both fluoxetine and sertraline discussed above. Perhaps the mild anticholinergic actions of paroxetine contribute to this clinical profile (Figure 7-18). Paroxetine also has weak norepinephrine transporter (NET) inhibitory properties, which could contribute to its efficacy in depression,

especially at high doses. The advantages of paroxetine M1 NET SERT SERT NOS Figure 7-18 Paroxetine. In addition to serotonin reuptake inhibition, paroxetine has mild anticholinergic actions (M1), which can be calming or possibly sedating; weak norepinephrine transporter (NET) inhibition, which may contribute to further antidepressant actions; and inhibition of the enzyme nitric oxide synthase (NOS), which may contribute to sexual dysfunction.

dual serotonin plus norepinephrine reuptake inhibiting properties, or SNRI actions, are discussed below in the section on SNRIs. It is possible that weak to moderate NET inhibition of paroxetine may contribute importantly to its antidepressant actions. Paroxetine also inhibits the enzyme nitric oxide synthase, which could theoretically contribute to sexual dysfunction, especially in men. Paroxetine is also notorious for causing withdrawal reactions upon sudden discontinuation, with symptoms such as akathisia, restlessness, gastrointestinal symptoms, dizziness, and tingling, especially when suddenly discontinued from long-term high-dose treatment. This is possibly due not only to SERT inhibition properties, since all SSRIs can cause discontinuation reactions, but also to anticholinergic rebound when paroxetine is rapidly discontinued. Paroxetine is available in a controlled-release formulation, which may mitigate some of its side effects, including discontinuation reactions. Fluvoxamine: An SSRI with σ1 Receptor Binding Properties This SSRI was among the first to be launched for the treatment of depression worldwide, but was never officially approved for depression in the US, so it has been considered more of an agent for the treatment of OCD in the US. Like sertraline, fluvoxamine binds at σ1 sites, but this action is more potent for fluvoxamine than for sertraline (Figure 7-19). The physiological function of σ1 sites is still a mystery, and thus sometimes called the “sigma enigma,” but has been linked both to anxiety and psychosis. Preclinical studies suggest that fluvoxamine fluvoxamine SERT Figure 7-19 Fluvoxamine. Fluvoxamine’s secondary properties include actions at σ1 receptors, which may be anxiolytic as well as beneficial for psychotic depression. Chapter 7: Treatments for Mood Disorders may be an agonist at σ1 receptors, and that this property may contribute an additional pharmacological action to help explain fluvoxamine’s well-known anxiolytic properties. Fluvoxamine also has shown therapeutic activity in both psychotic and delusional depression, where it, like sertraline, may have advantages over other SSRIs. Fluvoxamine is now available as a controlled-release formulation, which makes once-daily administration possible, unlike immediate-release fluvoxamine, whose shorter half-life often requires twice-daily administration. In addition, recent trials of controlled-release fluvoxamine show impressive remission rates in both OCD and social anxiety disorder, as well as possibly less peak-dose sedation. Citalopram: An SSRI with a “Good” and a “Bad” Enantiomer This SSRI is comprised of two enantiomers, R and S, which are mirror images of each other (Figure 7-20). The mixture of these enantiomers is known as racemic citalopram, or commonly just as citalopram, and has mild antihistamine properties that reside in the R enantiomer. Racemic citalopram is generally one of the better-tolerated SSRIs, and has favorable findings in the treatment of depression in the elderly, but has a somewhat inconsistent therapeutic action at the lowest dose, often requiring dose increase to optimize treatment. citalopram: R+S citalopram H1 R citalopram S citalopram Figure 7-20 Citalopram. Citalopram consists of two enantiomers, R and S. Some pharmacological evidence suggests that the R enantiomer may be pharmacologically active at SERTs in a manner that does not inhibit SERTs but actually interferes with the ability of the active S enantiomer to inhibit SERTs. The R enantiomer also has weak antihistamine properties. 295

S-citalopram Figure 7-21 Escitalopram The R and S enantiomers of citalopram are mirror images of each other but have slightly different clinical properties. The R enantiomer is the one with weak antihistamine properties; the R and S enantiomers may also differ in their effects at the serotonin transporter. The S enantiomer of citalopram has been developed and marketed as escitalopram. However, dose increase is limited due to the potential of QTc prolongation at higher doses. These findings all suggest that it is not favorable for citalopram to contain the R enantiomer. In fact, some pharmacological evidence suggests that the R enantiomer may be pharmacologically active at SERTs in a manner that does not inhibit SERTs but actually interferes with the ability of the active S enantiomer to inhibit SERTs. This could lead to reduced SERT inhibition, reduced synaptic 5HT, and possibly reduced net therapeutic actions, especially at low doses. Escitalopram: The Quintessential SSRI The solution to improving the properties of racemic citalopram is to remove the unwanted R enantiomer. The resulting drug is known as escitalopram, as it is comprised of only the pure active S enantiomer (Figure 7-21). This maneuver appears to remove the antihistaminic properties and there are no higher dose restrictions to avoid QTc prolongation. In addition, removal of the potentially interfering R enantiomer makes the lowest dose of escitalopram more predictably efficacious. Escitalopram is therefore the SSRI for which pure SERT inhibition is most likely to explain almost all of its pharmacological actions. Escitalopram is considered perhaps the best-tolerated SSRI, with the fewest cytochrome P450 (CYP450)-mediated drug interactions. Serotonin Partial Agonist Reuptake Inhibitors (SPARIs) Vilazodone combines SERT inhibition with 5HT1A partial agonism. For this reason, vilazodone is called vilazodone 5HT1A SERT SERT Figure 7-22 Vilazodone. Vilazodone is a partial agonist at the serotonin 1A receptor and also inhibits serotonin reuptake; thus, it is referred to as a serotonin partial agonist reuptake inhibitor (SPARI). a SPARI (serotonin partial agonist reuptake inhibitor) (Figure 7-22). The combination of serotonin reuptake inhibition with 5HT1A partial agonism has long been known by clinicians to enhance the unipolar antidepressant properties and tolerability of SSRIs/SNRIs in some patients (e.g., adding the 5HT1A partial agonist buspirone [Chapter 8 on anxiety]; the serotonin 1A/ dopamine 2 partial agonists aripiprazole, brexpiprazole, or cariprazine [Chapter 5]; or the serotonin/dopamine antagonist with 5HT1A partial agonist properties, quetiapine). With vilazodone this combination mechanism is achieved with only one drug, avoiding drug interactions and various off-target receptor actions that may be undesired with the other drugs listed. In animal models, adding 5HT1A partial agonism to SSRIs causes more immediate and robust elevations of brain 5HT levels than SSRIs do alone. This is thought to be due to the fact that 5HT1A partial agonists are a type of “artificial serotonin,” selective especially for presynaptic somatodendritic 5HT1A autoreceptors, and that 5HT1A partial agonist action occurs immediately after the drug is given (Figure 7-23). Thus, 5HT1A immediate partial agonist actions are theoretically additive or synergistic with simultaneous SERT inhibition (Figure 7-23) since this leads to faster and more robust actions at 5HT1A somatodendritic autoreceptors (Figure 7-24) than with SERT inhibition alone (Figure 7-12), including their downregulation (Figure 7-25). This hypothetically

1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A SPARI action: first, about half of SERTs and half of 5HT1A receptors are occupied immediately 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A 1A SPARI action: second, 5HT increases at 5HT1A somatodendritic receptors on the left causes faster and more robust elevation of synaptic 5HT (Figure 7-26) than possible with SSRIs alone (Figure 7-14). In addition, 5HT1A partial agonism with vilazodone’s SPARI mechanism occurs immediately at postsynaptic 5HT1A receptors (Figure 7-26), with actions at these receptors that are thus faster and with a different type of stimulation compared to the delayed full agonist actions of Chapter 7:

Treatments for Mood Disorders Figure 7-23 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 1. When a SPARI is administered, about half of serotonin transporters (SERTs) and half of serotonin 1A (5HT1A) receptors are occupied immediately. 5HT1A autoreceptor 1A SERT SPARI 1A 1A 1A 1A 1A 2A 2C 6 E Figure 7-24 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 2. Blockade of the serotonin transporter (SERT) causes serotonin to increase initially in the somatodendritic area of the serotonin neuron (left). 1A 1A 1A 1A 1A 2A 2C 6 E serotonin itself when increased by SERT inhibition alone (Figure 7-14). The downstream actions of 5HT1A receptors that lead to enhanced dopamine release (Figure 7-27) may be hypothetically responsible for enhanced antidepressant and precognitive effects (see Chapter 5 and Figure 5-22). The addition of 5HT1A partial agonist actions to SERT inhibition may also account for the observed reduction 297

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-25 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 3. The consequence of serotonin increasing in the somatodendritic area of the serotonin (5HT) neuron is that the somatodendritic 5HT1A autoreceptors desensitize or downregulate (red circle). 1A 1A 1A 1A 1A E 1A 1A 1A 1A 1A 2A 2C 6 SPARI action: third, 5HT actions on the left cause 5HT1A autoreceptors to desensitize/downregulate Figure 7-26 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 4. Once the somatodendritic receptors downregulate, there is no longer inhibition of impulse flow in the serotonin (5HT) neuron. Thus, neuronal impulse flow is turned on. The consequence of this is release of 5HT in the axon terminal (red circle). 1A 1A 1A 1A 1A E 1A 1A 1A 1A 1A 2A 2C 6 SPARI action: fourth, neuronal firing and serotonin release are disinhibited at the synapse on the right in sexual dysfunction and the relative lack of weight gain seen in patients treated with vilazodone. Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs) SNRIs combine the robust SERT inhibition of the SSRIs with various degrees of inhibition of the norepinephrine transporter (NET) (Figures 7-28 through 7-32). Theoretically, there should be some therapeutic advantage of adding NET inhibition to SERT inhibition, since one mechanism may add efficacy to the other mechanism by widening the reach of these drugs to both the serotonin and the norepinephrine monoamine neurotransmitter systems throughout more brain regions (see Chapter 6 and Figures 6-38 and 6-40). A practical indication that

Chapter 7: Treatments for Mood Disorders Figure 7-27 Mechanism of action of serotonin partial agonist reuptake inhibitors (SPARIs), part 5. Finally, once the SPARIs have blocked the serotonin transporter (SERT), increased somatodendritic serotonin (5HT), desensitized somatodendritic 5HT1A autoreceptors, turned on neuronal impulse flow, and increased release of 5HT from axon terminals, the final step (shown here, red circle) may be the desensitization of postsynaptic 5HT receptors. This timeframe correlates with antidepressant action. In addition, the addition of 5HT1A partial agonism may lead to downstream enhancement of dopamine (DA) release, which may mitigate sexual dysfunction. 1A 5HT1A autoreceptor SERT SPARI 1A 1A 1A 1A 2A 2C 6 SPARI action: finally, antidepressant actions begin, and downstream enhancement of DA release may mitigate sexual dysfunction DA 1A 1A 1A 1A 1A Figure 7-28 Venlafaxine and desvenlafaxine. Venlafaxine inhibits both the serotonin transporter (SERT) and the norepinephrine transporter (NET), thus combining two therapeutic mechanisms in one agent. Venlafaxine's serotonergic actions are present at low doses, while its noradrenergic actions are progressively enhanced as dose increases. Venlafaxine is converted to its active metabolite, desvenlafaxine, by CYP450 2D6. Like venlafaxine, desvenlafaxine inhibits reuptake of serotonin and norepinephrine, but its NET actions

are greater relative to its SERT actions compared to venlafaxine. Venlafaxine administration usually results in plasma levels of venlafaxine that are about half those of desvenlafaxine; however, this can vary depending on genetic polymorphisms of CYP450 2D6 and if patients are taking drugs that are inhibitors or inducers of CYP450 2D6. Thus, the degree of NET inhibition with venlafaxine administration may be unpredictable. Desvenlafaxine has now been developed as a separate drug. It has relatively greater norepinephrine reuptake inhibition than venlafaxine but is still more potent at the SERT. CYP 2D6 SERT NET SERT SERT NET SERT venlafaxine desvenlafaxine Figure 7-29 Duloxetine. Duloxetine inhibits both the serotonin transporter (SERT) and the norepinephrine transporter (NET). Its noradrenergic actions may contribute to efficacy for painful physical symptoms. duloxetine SERT NET SERT dual monoamine mechanisms may lead to more efficacy is the finding that the SNRI venlafaxine frequently seems to have greater unipolar antidepressant efficacy as the dose increases, theoretically due to recruiting more and more NET inhibition as the dose is raised (i.e., the noradrenergic “boost”). Clinicians and experts currently debate whether remission rates are higher with SNRIs compared to SSRIs or whether SNRIs are more helpful in depressed patients who fail to respond to SSRIs than are other options. One area where SNRIs have established clear efficacy but SSRIs have not is in the treatment of pain. NET Inhibition Increases Dopamine in the Prefrontal Cortex Although SNRIs are commonly called “dual action” serotonin–norepinephrine agents, they actually have

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-30 Milnacipran. Milnacipran inhibits both the serotonin transporter (SERT) and the norepinephrine transporter (NET) but is a more potent inhibitor of NET than SERT. Its robust NET inhibition may contribute to efficacy for painful physical symptoms. Milnacipran consists of two enantiomers: S (levo) and R (dextro), with S as the more active enantiomer. SERT NET NET milnacipran: R+S milnacipran SERT SERT S-milnacipran (levo) R-milnacipran (dextro) Figure 7-32 SNRI actions. The acute dual actions of the serotonin–norepinephrine reuptake inhibitors (SNRIs) are shown. Both the serotonin reuptake inhibitor portion of the SNRI molecule (left panel) and the norepinephrine reuptake inhibitor portion of the SNRI molecule (right panel) are inserted into their respective reuptake pumps. Consequently, both pumps are blocked, and synaptic serotonin and norepinephrine are increased. SNRI Action Figure 7-31 Levomilnacipran. The R and S enantiomers of milnacipran are mirror images of each other; the S enantiomer is the active enantiomer. The S enantiomer of milnacipran has been developed and marketed as levomilnacipran. SERT NET levomilnacipran: S-milnacipran SERT S-milnacipran (levo)

a third action on dopamine (DA) in the prefrontal cortex, but not elsewhere in the brain. Thus, they are not “full” triple action agents since they do not inhibit the DA transporter (DAT) except at doses beyond the clinical range, but SNRIs can perhaps be considered to have “two-and-a-half actions,” and not just two. That is, SNRIs not only boost serotonin and norepinephrine (NE) throughout the brain (Figure 7-32), but they also boost DA specifically in the prefrontal cortex (Figure 7-33). This third mechanism of boosting DA in an important area of the brain associated with several symptoms of depression should add another theoretical advantage to the pharmacology of SNRIs and to their efficacy in the treatment of major depression. How does NET inhibition boost DA in the prefrontal cortex? The answer is illustrated in Figure 7-33. In the prefrontal cortex, SERTs and NETs are present in abundance on serotonin and NE nerve terminals, respectively, but there are very few DATs on DA nerve terminals in this part of the brain (Figure 7-33, see also Chapter 4 and Figure 4-9A). The consequence of this lack of DATs in the prefrontal cortex is that once DA is released there,

it is free to cruise away from the synapse (Figure 7-33A). The diffusion radius of DA is thus wider (Figure 7-33A) than the diffusion radius of NE in the prefrontal cortex (Figure 7-33B) since there are NETs at the NE synapse (Figure 7-33B) but no DAT at the DA synapse (Figure 7-33A). This arrangement may enhance the regulatory importance of DA in the prefrontal cortex functioning, since DA in this part of the brain can interact with DA receptors not only at its own synapse, but at a distance, perhaps enhancing the ability of DA to regulate cognition in an entire area within its diffusion radius, not just at a single synapse. Dopamine action is therefore not terminated by DAT in the prefrontal cortex to any significant extent, but by two other mechanisms. That is, DA diffuses away from the DA synapse until it either encounters the enzyme COMT (catechol-O-methyltransferase), which degrades it (see Chapter 4 and Figure 4-3) or until it encounters a NET, which transports it into the NE neuron (Figure 7-33A). NETs in fact have a greater affinity for DA than they do for NE, so they will pump DA as well as NE into NE nerve terminals, halting the action of either. What is interesting is to see what happens when there is NET inhibition in the prefrontal cortex. As expected, NET inhibition enhances synaptic NE levels and increases the diffusion radius of NE (Figure 7-33B). Somewhat surprising may be that NET inhibition also enhances DA levels and increases DA's diffusion radius (Figure Chapter 7: Treatments for Mood Disorders Normal DA Release in PFC: No DAT, Diffuses to NET NE neuron NET DA neuron "normal" DA diffusion A "normal" NE diffusion NET Blocked in PFC: NE increases NET block increases NE diffusion B NET Blocked in PFC: DA increases NE neuron "normal" DA diffusion NET block increases DA diffusion DA neuron C Figure 7-33 Norepinephrine transporter blockade and dopamine in the prefrontal cortex. (A) Although there are abundant serotonin transporters (SERTs) and norepinephrine transporters (NETs) in the prefrontal cortex (PFC), there are very few dopamine transporters (DATs). This means that dopamine (DA) can diffuse away from the synapse and therefore exert its actions within a larger radius. Dopamine's actions are terminated at norepinephrine (NE) axon terminals, because DA is taken up by NETs. (B) NET blockade in the PFC leads to an increase in synaptic NE, thus increasing NE's diffusion radius. (C) Because NET takes up DA as well as NE, NET blockade also leads to an increase in synaptic DA, further increasing its diffusion radius. Thus, agents that block NET increase NE throughout the brain and both NE and DA in the PFC. 301

 7-33C). The bottom line is that NET inhibition increases both NE and DA in the prefrontal cortex. Thus, SNRIs have two-and-a-half mechanisms: boosting serotonin throughout the brain, boosting NE throughout the brain, and boosting DA in the prefrontal cortex (but not in other DA projection areas). Venlafaxine Depending upon the dose, venlafaxine has different degrees of inhibition of serotonin reuptake (most potent and robust even at low doses) versus NE reuptake (moderate potency and robust only at higher doses) (Figure 7-28). However, there are no significant actions on other receptors. It remains controversial whether venlafaxine or other SNRIs have greater efficacy in unipolar major depression than SSRIs, either in terms of enhanced remission rates, more robust sustained remission over long-term treatment, or greater efficacy for treatment-resistant unipolar depression, but this does seem plausible given two mechanisms and the boosting of two monoamines. Venlafaxine is approved and widely used for several anxiety disorders as well. Adding NET inhibition likely accounts for two side effects of venlafaxine in some patients: sweating and elevated blood pressure. Venlafaxine is available as an extended-release formulation, which not only allows for once-daily administration but also significantly reduces side effects, especially nausea. In contrast to several other psychotropic drugs available in controlled-release formulations, extended-release venlafaxine is a considerable improvement over the immediate-release formulation, which has fallen into little or no use because

of unacceptable nausea and other side effects, especially when immediate-release venlafaxine is started or when it is stopped. However, venlafaxine even in controlledrelease formulation can cause withdrawal reactions, sometimes quite bothersome, especially after sudden discontinuation from high-dose long-term treatment. Nevertheless, the controlled-release formulation is highly preferred because of enhanced tolerability. Desvenlafaxine Venlafaxine is a substrate for CYP450 2D6, which converts it to an active metabolite desvenlafaxine (Figure 7-28). Desvenlafaxine has greater NET inhibition relative to SERT inhibition compared to venlafaxine. Normally, after venlafaxine administration, the plasma levels of venlafaxine are about half of those for desvenlafaxine. However, this is highly variable, depending upon whether the patient is taking another drug that is a CYP450 2D6 inhibitor, which shifts the plasma levels towards more venlafaxine and less desvenlafaxine, also reducing the relative amount of NET inhibition. Variability in plasma levels of venlafaxine versus desvenlafaxine is also due to genetic polymorphisms for CYP450 2D6, such that poor metabolizers will shift the ratio of these two drugs towards more parent venlafaxine and away from the active metabolite desvenlafaxine, and thus reduce the relative amount of NET inhibition. As a result of these considerations, it can be somewhat unpredictable how much NET inhibition a given dose of venlafaxine will have in a given patient at a given time, whereas this is more predictable for desvenlafaxine. Expert clinicians have learned to solve this problem with skilled dose titration of venlafaxine, but the development of desvenlafaxine as a separate drug may also solve this problem, with less need for dose titration and more consistent NET inhibition at a given dose across all patients. Duloxetine This SNRI, characterized pharmacologically by slightly more potent SERT than NET inhibition (Figure 7-29), has transformed how we think about depression and pain. Classic teaching was that depression caused pain that was psychic (as in “I feel your pain”) and not somatic (as in “ouch”), and that psychic pain was secondary to emotional suffering in depression; therefore, it was thought, anything that made depression better would make psychic pain better nonspecifically. Somatic pain was thus not thought to be caused by depression, although depression could supposedly make it worse, and classically somatic pain was not treated with drugs for depression. Studies with duloxetine have changed all this. Not only does this SNRI relieve unipolar depression in the absence of pain, but it also relieves pain in the absence of depression. All sorts of pain are improved by this SNRI, from diabetic peripheral neuropathic pain, to fibromyalgia, to chronic musculoskeletal pain such as that associated with osteoarthritis and low back problems, and more. These findings of the efficacy of duloxetine for multiple pain syndromes have also validated that painful physical (somatic) symptoms are a legitimate set of symptoms that accompany depression and are not just a form of emotional pain. The use of SNRIs such as duloxetine in pain syndromes is discussed in Chapter 9. So, duloxetine has established efficacy not only in unipolar depression and in chronic pain, but also in patients with chronic painful physical

symptoms of unipolar depression. Painful physical symptoms are frequently ignored or missed by patients and clinicians alike in the setting of unipolar major depression, and until recently, the link of these symptoms to major depression was not well appreciated, in part because painful physical symptoms are not included in the list of symptoms for the formal diagnostic criteria for depression (see Chapter 6 and Figure 6-1). Nevertheless, it is now widely appreciated that painful physical symptoms are frequently associated with a major depressive episode, and are also one of the leading residual symptoms after initial treatment with drugs for depression (Figure 7-5). It appears that the dual SNRI actions of duloxetine and other SNRIs are superior to the selective serotonergic actions of SSRIs for treatment of conditions such as neuropathic pain of diabetes and chronic

painful physical symptoms associated with depression. The role of NET inhibition seems to be critical for the treatment not only of painful conditions without depression, but also for painful physical symptoms associated with depression. Duloxetine has also shown efficacy in the treatment of cognitive symptoms of depression that are prominent in geriatric depression, possibly exploiting the pro-noradrenergic and pro-dopaminergic consequences of NET inhibition in the prefrontal cortex (see Figure 7-33). Duloxetine can be given once a day, but this is usually only a good idea after the patient has had a chance to become tolerant to it after initiating it at twice-daily dosing, especially during titration to higher doses. Duloxetine may have a lower incidence of hypertension and milder withdrawal reactions than venlafaxine. Milnacipran Milnacipran is the first SNRI marketed in Japan and many European countries such as France, where it is currently marketed as a drug for unipolar depression. In the US, milnacipran is not approved for unipolar depression, but is approved for fibromyalgia. Interestingly, it is the other way around in Europe: milnacipran is approved for unipolar depression but not approved for the treatment of fibromyalgia. Milnacipran is a bit different from other SNRIs in that it is a relatively more potent NET than SERT inhibitor (Figure 7-30), whereas the others are more potent SERT than NET inhibitors (Figures 7-28 and 7-29). This unique pharmacological profile may explain milnacipran's somewhat different clinical profile compared to other SNRIs. Since noradrenergic actions may be equally or more important for treatment of painrelated conditions compared to serotonergic actions, the Chapter 7: Treatments for Mood Disorders robust NET inhibition of milnacipran suggests that it may be particularly useful in chronic pain related conditions, not just fibromyalgia where it is approved, but possibly as well for the painful physical symptoms associated with unipolar depression and chronic neuropathic pain. Milnacipran's potent NET inhibition also suggests a potentially favorable pharmacological profile for the treatment of cognitive symptoms, including cognitive symptoms of unipolar depression as well as cognitive symptoms frequently associated with fibromyalgia, sometimes called "fibro-fog." Other clinical observations possibly linked to milnacipran's robust NET inhibition are that it can be more energizing and activating than other SNRIs. Common residual symptoms after treatment with an SSRI include not only cognitive symptoms, but also fatigue, lack of energy, and lack of interest, among other symptoms (Figure 7-5). NET inhibition may be related to observations that milnacipran may cause more sweating and urinary hesitancy than some other SNRIs. For patients with urinary hesitancy, generally due theoretically to robust pro-noradrenergic actions at bladder α1 receptors, an α1 antagonist can reduce these symptoms. Milnacipran must generally be given twice daily due to its shorter half-life. Levomilnacipran Milnacipran is actually a racemic mixture of two enantiomers (Figure 7-30). The S or levo enantiomer is the active enantiomer (Figure 7-31) and has been independently developed for unipolar major depressive disorder in the US, where it is mostly available. Like racemic milnacipran, levomilnacipran has greater NET inhibition than SERT inhibition and may target fatigue and lack of energy as potential clinical advantages. Also, it is dosed in a controlled-release formulation, so, unlike racemic milnacipran, can be given only once a day. Norepinephrine–Dopamine Reuptake Inhibitors (NDRIs): Bupropion For many years, the mechanism of action of bupropion has been unclear and still remains somewhat controversial. Bupropion itself only has weak reuptake blocking properties for dopamine (DAT inhibition), and for norepinephrine (NET inhibition) (Figures 7-34 and 7-35). No other specific or potent pharmacological actions have been consistently identified for this agent. Bupropion's actions both as a drug for unipolar depression and upon norepinephrine and dopamine neurotransmission, however, have always appeared to be more powerful than these weak properties could explain, 303

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-34 Norepinephrine–dopamine reuptake inhibitor (NDRI). The prototypical norepinephrine–dopamine reuptake inhibitor (NDRI) is bupropion. Bupropion has weak blocking properties for the dopamine transporter (DAT) and for the norepinephrine transporter (NET). Its antidepressant actions may be explained in part by the more potent inhibitory properties of its metabolites. NDRI DAT NET Figure 7-35 NDRI actions. The norepinephrine reuptake inhibitor portion of the NDRI molecule (left panel) and the dopamine reuptake inhibitor portion of the NDRI molecule (right panel) are inserted into their respective reuptake pumps. Consequently, both pumps are blocked, and synaptic norepinephrine and dopamine are increased. NDRI Action leading to proposals that bupropion acts rather vaguely as an adrenergic modulator of some type. Bupropion is metabolized to a number of active metabolites, some of which are not only more potent NET inhibitors than bupropion itself and equally potent DAT inhibitors, but are also concentrated in the brain. In some ways, therefore, bupropion is both an active drug and a precursor for other active drugs (i.e., a prodrug for multiple active metabolites). The most potent of these is the + enantiomer of the 6-hydroxy metabolite of bupropion, also known as radafaxine. Can the net effects of bupropion on NETs (Figure 7-36A and 7-36B) and DATs (Figure 7-36C) account for its clinical actions in depressed patients at therapeutic doses? If one believes that 90% transporter occupancy of DATs and NETs are required for drugs for antidepressant actions, the answer would be "no." Human positron emission tomography (PET) scans suggest that as little as 10–15% and perhaps no more than 20–30% of striatal DATs may be occupied at therapeutic doses of bupropion. NET occupancy would be expected to be in this same range. Is this enough to explain bupropion's antidepressant actions?

Chapter 7: Treatments for Mood Disorders Figure 7-36 NDRI actions in prefrontal cortex and striatum. Norepinephrine–dopamine reuptake inhibitors (NDRIs) block the transporters for both norepinephrine (NETs) and dopamine (DATs). (A) NET blockade in the prefrontal cortex leads to an increase in synaptic norepinephrine (NE), thus increasing NE's diffusion radius. (B) Because the prefrontal cortex lacks DATs, and NETs transport dopamine (DA) as well as NE, NET blockade also leads to an increase in synaptic DA in the prefrontal cortex, further increasing DA's diffusion radius. Thus, despite the absence of DAT in the prefrontal cortex, NDRIs still increase DA there. (C) DAT is present in the striatum, and thus DAT inhibition increases DA diffusion there. C A B "normal" DA diffusion "normal" DA diffusion NET blockade increases DA diffusion "normal" NE diffusion NET blockade increases NE diffusion DAT blockade increases DA diffusion DAT DA neuron NE neuron DA neuron NDRI action in prefrontal cortex: NET blockade increases NE and DA NDRI action in striatum: DAT blockade increases DA Whereas it is clear from many research studies that SSRIs must be dosed to occupy a substantial fraction of SERTs, perhaps up to 80% or 90% of these transporters, in order to be effective drugs for depressions, this is far less clear for NET or DAT occupancy, particularly in the case of drugs with an additional pharmacological mechanism that may be synergistic with NET or DAT inhibition. That is, when most SNRIs are given in doses that occupy 80–90% of SERTs, substantially fewer NETs are occupied, yet there is evidence of both additional therapeutic actions and NE-mediated side effects of these agents with perhaps as little as 50% NET occupancy. Furthermore, there appears to be such a thing as "too much DAT occupancy." That is, when 50% or more of DATs are occupied rapidly and briefly, this can lead to unwanted clinical actions, such as euphoria and reinforcement (see discussion of the mysterious DATs in Chapter 11 on attention deficit hyperactivity disorder [ADHD] treatment). In fact, rapid, short-lasting, and high degrees of DAT occupancy are the pharmacological characteristics of abusable stimulants such as cocaine (discussed in Chapter 13 on drug abuse and reward). When

50% or more of DATs are occupied more slowly and in a more long-lasting manner, especially with

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY controlled-release formulations, DAT inhibitors are less abusable and more useful for ADHD (see Chapter 11). The issue to be considered here is whether a low level of slow-onset and long-lasting DAT occupancy is the desirable solution for the DAT mechanism to be useful as a drug for unipolar depression: thus, not too much or too fast DAT inhibition and therefore abusable; not too little DAT inhibition and therefore ineffective; but just enough DAT inhibition with slow enough onset and long enough duration of action to make it an effective drug for unipolar depression. The fact that bupropion is not known to be particularly abusable, is not a scheduled substance, yet is proven effective for treating nicotine addiction, is consistent with the possibility that it is occupying DATs in the striatum and nucleus accumbens in a manner sufficient to mitigate craving but not sufficient to cause abuse (Figure 7-36C). This use of bupropion for smoking cessation is discussed further in Chapter 13 on drug abuse and reward. Perhaps this low level of DAT occupancy (Figure 7-36C) is also how bupropion works in unipolar depression, combined with an equally low action on NETs (Figure 7-36A and 7-36B). Bupropion was originally marketed only in the US as an immediate-release dosage formulation for three-times-daily administration as a drug for unipolar depression. Development of a twice-daily formulation (bupropion SR) and then a once-daily formulation (bupropion XL) have not only reduced the frequency of seizures at peak plasma drug levels, but have also increased convenience and enhanced compliance as well. Thus, the use of immediate-release bupropion is all but abandoned in favor of once-daily administration. Bupropion is generally activating or even stimulating. Bupropion does not appear to cause the bothersome sexual dysfunction that frequently occurs with many drugs for unipolar depression that act by SERT inhibition, probably because bupropion lacks a significant serotonergic component to its mechanism of action. Thus, bupropion has proven to be a useful drug for unipolar depression not only for patients who cannot tolerate the serotonergic side effects of SSRIs, but also for patients whose depression does not respond to serotonergic boosting by SSRIs. Consistent with its pharmacological profile, bupropion is especially targeted at the symptoms of the "dopamine deficiency syndrome" and "reduced positive affect" (see Figure 6-41), including improvement in the symptoms of loss of happiness, joy, interest, pleasure, energy, enthusiasm, alertness, and self-confidence. Almost every active clinician knows that patients who have residual symptoms of reduced positive affect following treatment with an SSRI or an SNRI, or who develop these symptoms as a side effect of an SSRI or SNRI, frequently benefit from switching to bupropion or from augmenting their SSRI or SNRI treatment with bupropion. The combination of bupropion with an SSRI or an SNRI has a theoretical rationale as a strategy for covering the entire symptom portfolio from symptoms of reduced positive affect to symptoms of increased negative affect (Figure 6-41). Bupropion combined with the μ-opioid antagonist naltrexone is approved for the treatment of obesity and mentioned in Chapter 13 on impulsivity/compulsivity syndromes. Bupropion combined with the NMDA (Nmethyl-D-aspartate) antagonist dextromethorphan is in late-stage clinical trials both for depression (mentioned below) and for agitation in Alzheimer disease (discussed in Chapter 12 on dementia). Agomelatine Agomelatine (Figure 7-37) is approved to treat unipolar depression in many countries outside of the US. It has agonist actions at melatonin 1 (MT1) and melatonin 2 (MT2) receptors and antagonist actions at 5HT2C receptors (Figure 7-37). As discussed above in the section agomelatine 5HT2B 5HT2C MT1 MT2 Figure 7-37 Agomelatine. Endogenous melatonin is secreted by the pineal gland and mainly acts in the suprachiasmatic nucleus to regulate circadian rhythms. There are three types of receptors for melatonin: 1 and 2 (MT1 and MT2), which are both involved in sleep, and 3, which is actually the enzyme NRH–quinine

oxidoreductase 2 and not thought to be involved in sleep physiology. Agomelatine is not only a melatonin 1 and 2 receptor agonist, but is also a 5HT2C and 5HT2B receptor antagonist, and is available to treat depression in countries outside of the US.

Chapter 7: Treatments for Mood Disorders Figure 7-38 Agomelatine releases norepinephrine and dopamine in the prefrontal cortex. Normally, serotonin binding at 5HT2C receptors on γ-aminobutyric acid (GABA) interneurons in the brainstem inhibits norepinephrine (NE) and dopamine (DA) release in the prefrontal cortex. When a 5HT2C antagonist such as agomelatine binds to 5HT2C receptors on GABA interneurons (bottom red circle), it prevents serotonin (5HT) from binding there and thus prevents inhibition of NE and DA release in the prefrontal cortex; in other words, it disinhibits their release (top red circles). prefrontal cortex brainstem neurotransmitter centers raphe VTA locus coeruleus DA release NE release 5HT neuron NE neuron DA neuron GABA interneurons 5HT2C agomelatine Agomelatine Releases Norepinephrine and Dopamine in the Frontal Cortex agomelatine overactivation time (min) 60 100 200 180 agomelatine vehicle NE change from Basal (%) 60 180 time (min) DA change from Basal (%) 150 250 350 on fluoxetine, 5HT2C antagonist actions are a property of several drugs used to treat unipolar depression (agomelatine, fluoxetine, trazodone, mirtazapine, some tricyclic antidepressants) and bipolar depression (olanzapine and quetiapine). 5HT2C receptors are located in the midbrain raphe and prefrontal cortex where they regulate the release of dopamine and norepinephrine, an action thought to improve depressive symptoms (see Figure 7-38). 5HT2C receptors are also localized in the suprachiasmatic nucleus (SCN) of the hypothalamus, the brain's "pacemaker," where they interact with melatonin receptors also located there (Figure 7-39). Light is detected by the retina during the day, and this information travels to the SCN via the retinohypothalamic tract (Figure 7-39; see also Chapter 6 and Figures 6-36A and 6-36B), which normally synchronizes many circadian rhythms downstream from the SCN. For example, both melatonin receptors and

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-40 Mirtazapine and mianserin. Mirtazapine's primary therapeutic action is α2 antagonism. It also blocks three serotonin (5HT) receptors: 5HT2A, 5HT2C, and 5HT3. Finally, it blocks histamine 1 (H1) receptors. Mianserin has a similar binding profile to mirtazapine, the only difference being additional effects at α1 receptors. NaSSA: noradrenergic and specific serotonergic antidepressant. mianserin 5HT2C 5HT3 5HT2A 2A α H1 5HT2C 5HT3 5HT2A 2A α α H1 mirtazapine (NaSSA) mianserin as well, appears to resynchronize circadian rhythms, reverse the phase delay of depression, and thereby exert an antidepressant effect (Figure 7-39). Mirtazapine Mirtazapine (Figure 7-40) is marketed worldwide and, unlike almost every other drug for unipolar depression, it does not block any monoamine transporter. Instead, mirtazapine is a multifunctional drug with five principal mechanisms of action: 5HT2A, 5HT2C, 5HT3, α2-adrenergic, Figure 7-39 Agomelatine may resynchronize circadian rhythms. Agomelatine, which acts as an agonist at melatonin 1 and 2 receptors, may resynchronize circadian rhythms by acting as "substitute melatonin." Thus, even in the absence of melatonin production in the pineal gland, agomelatine can stimulate melatonin 1 and 2 receptors in the suprachiasmatic nucleus (SCN) to reset circadian rhythms. 5HT2C receptors are also present in the SCN and blocked by agomelatine. In addition, by blocking 5HT2C receptors in the ventral tegmental area (VTA) and locus coeruleus (LC), agomelatine promotes dopamine (DA) and norepinephrine (NE) release in the prefrontal cortex. SCN retinohypothalamic tract pineal gland agomelatine 7 am 7 am sleep sleep 11 pm 7 am 11 pm Healthy Control Depression VTA LC NE DA 5HT2C receptors fluctuate in a circadian manner in the SCN, with high receptor expression at night/dark and low receptor

expression in the day/light. That makes sense since melatonin is only secreted at night in the dark (see Chapter 6 and Figures 6-35 and 6-36B). In some patients with unipolar depression, however, circadian rhythms are “out of synch,” including low melatonin secretion at night among numerous other changes. Theoretically, agomelatine, by stimulating melatonin receptors in the SCN and simultaneously blocking 5HT2C receptors there

and H1 histamine antagonism. Two other α2 antagonists are marketed as drugs for depression in some countries (but not the US), namely mianserin (worldwide except US) and setiptiline (Japan). Unlike mirtazapine, mianserin also has potent α1 antagonist properties, which tend to mitigate its ability to enhance serotonergic neurotransmission so that this drug enhances predominantly noradrenergic neurotransmission, yet with associated 5HT2A, 5HT2C, 5HT3, and H1 antagonist properties (Figure 7-40). Clinical consequences of blocking H1 receptors have been discussed in Chapter 5 and illustrated in Figure 5-13A, showing that H1 antagonist actions are associated with sedation and weight gain. 5HT2A antagonist properties also have been discussed in Chapter 5 and illustrated in Figures 5-16 and 5-17, showing increases in downstream release of dopamine in the prefrontal cortex, potentially associated with antidepressant actions. 5HT2A antagonism also improves sleep, especially slow-wave sleep, which can be helpful in many depressed patients. 5HT2C antagonist actions were just explained in the preceding section and illustrated in Figure 7-38, showing enhanced release of norepinephrine and dopamine in the prefrontal cortex, which would theoretically improve depression. Here we explain the other actions of mirtazapine, notably α2 antagonist actions and 5HT3 antagonist actions. Some other drugs for unipolar depression also have potent α2 antagonist actions (Figure 5-35), including brexpiprazole (Figure 5-57) and quetiapine (Figure 5-45). Some other drugs for bipolar depression also have α2 antagonist actions, including quetiapine (Figure 5-45) and lurasidone (Figure 5-53). Another agent for treatment of unipolar depression that has potent 5HT3 antagonist properties is vortioxetine, discussed below.
Alpha-2 Antagonist Action Alpha-2 antagonism is another way to enhance the release of monoamines and exert an antidepressant action in unipolar depression. Recall that norepinephrine turns off its own release by interacting with presynaptic α2 autoreceptors on noradrenergic neurons (discussed in Chapter 6 and illustrated in Figures 6-14 through 6-16; see also Figure 7-41A and B on the right). Therefore, when an α2 antagonist is administered, norepinephrine can no longer turn off its own release and noradrenergic neurons are thus disinhibited from their axon terminals, such as those in the raphe and in the cortex as shown in Figure 7-41C on the right. The general principle of serotonin turning off serotonin release at serotonin 5HT1B autoreceptors (Figure 4-41 and Figure 7-41A compared to 7-41B on Chapter 7: Treatments for Mood Disorders the left) has already been discussed and is illustrated again here. However, there are also α2 “hetero” receptors on serotonin neurons (Figure 7-41A, B, C on the left). There are many cases where neurotransmitter release is controlled not only by their “own” autoreceptor, but also by presynaptic receptors for “another” neurotransmitter at heteroreceptors (Figure 7-41A; see also Figure 4-45 and discussion of presynaptic 5HT1B heteroreceptors on norepinephrine, dopamine, histamine, and acetylcholine neurons). The same phenomenon is shown in Figure 7-41B where not only is serotonin turning off serotonin release at its own 5HT1B presynaptic autoreceptor on the left hand part of the serotonin neuron, but also norepinephrine migrating from a norepinephrine terminal is turning off serotonin release via an α2 presynaptic heteroreceptor on the right hand part of the serotonin neuron. Norepinephrine is also turning off its own release via an α2 presynaptic receptor (Figure 7-41B on the right at the norepinephrine neuron). This sets up the situation whereby an α2 antagonist can have a dual effect, facilitating the release of both norepinephrine and serotonin

(Figure 7-41C). Not only does α2 antagonism disinhibit norepinephrine release (Figure 7-41C on the right), it also disinhibits serotonin release (Figure 7-41C on the left). Thus, α2 antagonism causes dual 5HT–NE action. This is something like the same net outcome as an SNRI but by an entirely different mechanism. Rather than blocking serotonin and norepinephrine presynaptic transporters, α2 antagonism "cuts the brake cable" of noradrenergic inhibition (NE stepping on the brake to prevent 5HT and NE release shown in Figure 7-41B is blocked in Figure 7-41C). These two mechanisms, monoamine transport blockade and α2 antagonism, are synergistic, so that blocking them simultaneously gives a much more powerful disinhibitory signal to these two neurotransmitters than if only one mechanism is blocked. For this reason, the α2 antagonist mirtazapine is often combined with SNRIs for treatment of cases that do not respond to an SNRI alone. This combination of mirtazapine with an SNRI is sometimes called "California rocket fuel" because of the potentially powerful drugs for depression blasting the patient out of the depths of depression. 5HT3 Antagonist Action The 5HT3 receptors best known to clinicians are perhaps those localized in the chemoreceptor trigger zone of the brainstem, where they mediate nausea and vomiting, especially in response to cancer chemotherapy, and 309

Figure 7-41 Alpha-2 antagonism increases serotonin and norepinephrine release in raphe and cortex. (A) On the left, a serotonergic neuron is shown with 5HT1B/D autoreceptors and α2-adrenergic heteroreceptors. On the right, a noradrenergic neuron is shown with presynaptic α2 autoreceptors. (B) 5HT1B/D autoreceptors and α2-adrenergic heteroreceptors on serotonergic neurons both function as "brakes" to shut off serotonin release when bound by their respective neurotransmitters (left). Likewise, when norepinephrine binds to α2 autoreceptors on the norepinephrine neuron, this shuts off further norepinephrine release (right). (C) Alpha-2 antagonists "cut the serotonin brake cable" when they block α2 presynaptic heteroreceptors, thus leading to enhanced serotonin release (left). Alpha-2 antagonists also "cut the norepinephrine brake cable" by blocking presynaptic α2 autoreceptors, leading to enhanced norepinephrine release (right). 5HT neuron A B NE neuron α2 α2 5HT1 B/D α2 α2 5HT1 B/D C α2 = α2 antagonist α2 5HT1 B/D

also those localized in the gastrointestinal tract itself, where they mediate nausea, vomiting, and diarrhea/ bowel motility when stimulated by serotonin, including when stimulated by serotonin that is a side effect of peripherally increased serotonin by SSRIs/SNRIs. Blocking these 5HT3 receptors can therefore protect against chemotherapy-induced nausea and vomiting as well as against serotonin-induced gastrointestinal side effects that can accompany agents that increase serotonin. More important to the mechanism of action of central 5HT3 antagonists such as mirtazapine and vortioxetine in the treatment of unipolar depression are the 5HT3 receptors in the brain that regulate the release of various neurotransmitters downstream in some brain circuits that mediate the symptoms of depression. 5HT3 receptors in the brain are usually localized on GABA (γ-aminobutyric acid) interneurons, and they are always excitatory. This means that when serotonin stimulates a 5HT3 receptor, it causes GABA to inhibit whatever neuron is downstream from it. This was shown for 5HT3–GABA interactions at glutamate neurons (Figure 4-49) and at acetylcholine and norepinephrine neurons (Figure 4-48). 5HT3 antagonism is a powerful disinhibitor of glutamate release (Figure 7-42) and of acetylcholine and norepinephrine (Figure 7-43), actions that theoretically release neurotransmitters downstream to have antidepressant action. Serotonin Antagonist/Reuptake Inhibitors (SARIs) The prototype drug that blocks serotonin 2A and 2C receptors as well as serotonin reuptake is trazodone, classified as a serotonin antagonist/reuptake

inhibitor (SARI) (Figure 7-44). Nefazodone is another SARI with robust 5HT2A antagonist actions and weaker 5HT2C antagonism and SERT inhibition, but is no longer commonly used because of rare liver toxicity (Figure 7-44). Trazodone is a very interesting agent, since it acts like two different drugs, depending upon the dose and the formulation. We discussed a very similar situation in Chapter 5 for quetiapine (Figure 5-46). A more complete picture of trazodone's binding properties has emerged from recent studies (Figures 7-44 and 7-45) and reflects that it is a serotonin antagonist not just at 5HT2A and 5HT2C receptors, but also at 5HT1D, 5HT2B, and 5HT7 receptors. In addition, trazodone has potent antagonist properties at α1B, α1A, α2C, and α2B receptors, H1 histamine receptors, and agonist actions at 5HT1A receptors (Figure 7-45). Because of these various pharmacological actions occur with varying potencies, Chapter 7: Treatments for Mood Disorders it means that trazodone will act predominantly via its highest-affinity receptor interactions at low doses, and will recruit its lower-affinity receptor actions at higher doses. Different Drug at Different Doses and at Different Delivery Rates? Trazodone is famous for its effectiveness and utility at low doses as a hypnotic (Figure 7-46). That is, doses of trazodone lower than those effective for antidepressant action are quite frequently used for insomnia. Hypnotic doses engage the receptors for which trazodone has the highest affinity and, amongst these, blockade is hypothetically linked to hypnotic actions (i.e., 5HT2A, α1 subtypes, and H1). Blocking 5HT2A receptors enhances slow-wave sleep, and blocking α1 subtypes and H1 receptors interferes with monoamine arousal mechanisms (discussed in Chapter 5 and illustrated in Figures 5-13 and 5-14). The best way to deliver a hypnotic is with a standard oral formulation that is immediate in onset, peaks quickly, and is out of the system by morning. Since insomnia is one of the most frequent residual symptoms of depression after treatment with an SSRI/ SNRI (discussed earlier in this chapter and illustrated in Figure 7-5), addition of a hypnotic is often necessary in treating patients with a major depressive episode. Not only can addition of a hypnotic potentially relieve the insomnia itself, it may also increase remission rates due to improvement of other symptoms such as loss of energy and depressed mood (Figure 7-5). Thus, the ability of low doses of trazodone to improve sleep in depressed patients has led to its popular use at low doses as an augmenting option for residual insomnia that persists after treatment with SSRIs/SNRIs. The original oral formulation of trazodone used for depression was short in duration, required multiple daily doses higher than hypnotic doses (Figure 7-47), and was associated with peak dose sedation after daytime doses, not an ideal profile for a drug for unipolar depression. Although trazodone's antidepressant actions at higher doses are undisputed as well as its lack of causing sexual dysfunction or weight gain, the presence of daytime sedation makes using trazodone at antidepressant doses in the standard oral formulation difficult in clinical practice. However, a once-daily controlled-release formulation with higher doses of trazodone is available for use in depression, which blunts peak plasma drug levels to reduce daytime sedation. These higher doses recruit additional known antidepressant receptor actions, including serotonin reuptake inhibition (Figures 7-10 311

Figure 7-42 5HT3 receptors regulate glutamate and

downstream neurotransmitters. Serotonin (5HT) binding at 5HT3 receptors on GABA interneurons is stimulatory; thus, it increases GABA release. GABA, in turn, inhibits glutamate pyramidal neurons, reducing glutamate output. Decreased release of excitatory glutamate means that there may be a resultant decrease in downstream release of neurotransmitters, since pyramidal neurons synapse with the neurons of most other neurotransmitters. Antagonism at the 5HT3 receptor removes GABA inhibition and thus

disinhibits pyramidal neurons. The increase in glutamate neurotransmission may in turn increase the downstream release of neurotransmitters. 5HT3 Antagonists Disinhibit Glutamate Release and Enhance the Release of Downstream Neurotransmitters to Improve Depression Prefrontal Cortex Raphe GABA 5HT Glu 5HT3 antagonist

3 + Serotonin at 5HT3 Receptors Regulates Glutamate Release and Downstream Neurotransmitters Prefrontal Cortex Raphe GABA 5HT

Glu Regulation of downstream release of DA, NE, ACh, HA Regulation of downstream release of DA, NE, ACh, HA non-parvalbumin positive, regular spiking, late spiking or bursting GABA interneuron

:

excitatory 5HT3 receptor inhibitory

.

Chapter 7: Treatments for Mood Disorders Figure 7-43 5HT3 receptors regulate norepinephrine and acetylcholine release. When serotonin (5HT) is released, it binds to 5HT3 receptors on

GABAergic neurons, which release GABA onto noradrenergic and cholinergic neurons, thus reducing release of norepinephrine (NE) and acetylcholine (ACh), respectively. Antagonism at the 5HT3 receptor removes GABA inhibition and disinhibits noradrenergic and cholinergic neurons, leading to release of norepinephrine and acetylcholine. 5HT3 Receptors Cause Inhibition of Norepinephrine and Acetylcholine Release 5HT3 Antagonists Enhance Norepinephrine and Acetylcholine Release Prefrontal Cortex Basal

Forebrain Locus Coeruleus Raphe 5HT ACh NE

GABA GABA GABA inhibits NE release GABA inhibits ACh release inhibition of NE release + + + 5HT 5HT Prefrontal Cortex Basal Forebrain Locus Coeruleus Raphe 5HT ACh NE + GABA GABA NE release ACh release + 5HT3 antagonist 5HT3 antagonist inhibition of ACh release non-parvalbumin positive, regular spiking, late spiking or bursting GABA interneuron excitatory 5HT3

receptor inhibitory

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-44 Serotonin antagonist/reuptake inhibitors (SARIs). Shown here are icons for two serotonin antagonist/reuptake inhibitors (SARIs): trazodone and nefazodone. These agents have a dual action, but the two mechanisms are different from the dual action of the serotonin–norepinephrine reuptake inhibitors (SNRIs). The SARIs act by potent blockade of serotonin 2A (5HT2A) receptors as well as dose-dependent blockade of serotonin 2C (5HT2C) receptors and the serotonin transporter (SERT). SARIs also block α1-adrenergic receptors. Trazodone has the unique properties of histamine 1 (H1) receptor antagonism and antagonism at multiple additional serotonin receptors. SERT SERT NET mianserin 5HT2C 5HT7 5HT2A 5HT1D 5HT2B 5HT1A α α H1 trazodone mianserin 5HT2C 5HT2A α nefazodone Figure 7-45 Trazodone affinity for different receptors. Trazodone has binding affinity for numerous receptor subtypes, but the potency varies. Thus, at low doses, trazodone may act predominantly via its highest-affinity receptor actions, with other properties becoming relevant only at higher doses. 1000 higher affinity target affinity Ki (nM) lower affinity 200 5HT2A 5HT1A 5HT2C Na-channel (rat) sigma (non-selective) 5HT7 5HT1B 5HT1D 5HT2B alpha 1B alpha 1A alpha 2C alpha 2B D3 D2 D1 SERT H1 through 7-15) and antagonist action at 5HT1D, 5HT2C, 5HT7, and α2 receptors, as well as 5HT1A agonist actions. The bottom line is that there are numerous potential mechanisms to cause monoamine neurotransmitter release and antidepressant actions at higher doses. Furthermore, with first-dose hypnotic actions, trazodone can exert its antidepressant actions with rapid onset and enhanced tolerability for some side effects compared to SSRIs/SNRIs. That is, SSRIs/SNRIs raise serotonin levels to act at all serotonin receptors, stimulating 5HT1A receptors for therapeutic actions while concomitantly stimulating 5HT2A receptors and 5HT2C receptors that theoretically cause the side effects of SSRIs including sexual dysfunction, insomnia, and activation/anxiety (Figure 7-48A). However, trazodone blocks the actions of serotonin at 5HT2A and 5HT2C receptors, accounting for its profile of lack of sexual dysfunction and reduction of anxiety and insomnia.

Trazodone for Depression: Trazodone for Insomnia: Multifunctional Neurotransmitter Antagonist Serotonin Antagonist/ Reuptake Inhibitor (SARI) α α 1 5HT1A α1 α1 5HT2A H1 5HT1D SERT trazodone 5HT2A 5HT2A mianserin 5HT2B 5HT2C 5HT7 dose for depression (150-600 mg) Trazodone IR vs. XR Given Once Nightly 2.2 1.8 1.6 1.4 1.2 mg/L 100 mg IR qhs minimum antidepressant concentration 0.8 0.65 75 mg IR qhs 0.5 0.3 50 mg IR qhs 0.1 23:30 23:30 4:00 8:00 12:00 16:00 20:00 hours Vortioxetine Vortioxetine is a drug approved for treating unipolar depression and which causes SERT inhibition as well as having antagonist actions at 5HT3 and 5HT7 receptors, with agonist actions at 5HT1A receptors and weak partial agonist to antagonist actions at 5HT1B/D receptors (Figure 7-49). This unique blend of pharmacological actions leads to downstream release of many different neurotransmitters as will be explained here, and these actions hypothetically lead to antidepressant effects in unipolar depression, characterized by robust proChapter 7: Treatments for Mood Disorders Figure 7-46 Trazodone at different doses. (Left) High doses that recruit saturation of the serotonin transporter (i.e., 150–600 mg) are required for trazodone to have therapeutic actions in depression. At this high dose, trazodone is a multifunctional serotonergic agent with antagonist actions at 5HT2A and 5HT2C receptors as well as additional serotonin receptors. Trazodone is also an α1 and histamine 1 (H1) antagonist at these

doses. (Right) At lower doses of trazodone (i.e., 25–150 mg), it does not saturate the serotonin transporter; it does, however, retain antagonist actions at 5HT2A, α1, and H1 receptors, with corresponding efficacy for insomnia. H1 H1 dose for insomnia (25-150 mg) Figure 7-47 Trazodone IR versus XR given once nightly. Shown here are steady-state estimates of the plasma trazodone levels from the hypnotic dosing of 50, 75, or 100 mg once nightly of trazodone immediate release (IR). Peak drug concentrations are reached rapidly with a similarly rapid fall off overnight. The minimum levels estimated for antidepressant actions of trazodone are reached transiently, if at all, by hypnotic dosing. By contrast, 300 mg of trazodone extended release (XR) given once nightly generates plasma levels that rise slowly and never fall below minimum antidepressant concentrations. Peak levels of trazodone XR at 300 mg are about the same as the peak levels of trazodone IR at 100 mg. 300 mg XR qhs cognitive actions, especially improving processing speed. The importance of cognitive symptoms in unipolar depression is discussed in Chapter 6 as the possible clinical consequence of loss of neurotrophic factors, synapses, and neurons (Figures 6-27 through 6-31). What is cognitive processing speed and what could be the mechanism by which vortioxetine improves this more than other antidepressants? “Cognition” is not a single, simple brain function and “cognitive dysfunction” is not a single, simple symptom. Cognitive impairment that can be measured as part of the symptom profile 315

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY 5HT2A SSRI 5HT1A SSRI Action sexual dysfunction insomnia anxiety 5HT2C A B antidepressant SARI SARI Action at 5HT Synapses 5HT2A 5HT1A sexual dysfunction insomnia anxiety 5HT2C antidepressant Figure 7-48 SSRI vs. SARI. (A) Inhibition of the serotonin transporter (SERT) by a selective serotonin reuptake inhibitor (SSRI) at the presynaptic neuron increases serotonin at all receptors, with 5HT1A-mediated antidepressant actions but also 5HT2A- and 5HT2Cmediated sexual dysfunction, insomnia, and anxiety. (B) SERT inhibition by a serotonin 2A antagonist/reuptake inhibitor (SARI) at the presynaptic neuron increases serotonin at 5HT1A receptors, where it leads to antidepressant actions. However, SARI action also blocks serotonin actions at 5HT2A and 5HT2C receptors, thus failing to cause sexual dysfunction, insomnia, or anxiety. In fact, these blocking actions at 5HT2A and 5HT2C receptors can improve insomnia and anxiety, and theoretically can exert antidepressant actions of their own. of a psychiatric disorder, and that can be targeted for improvement with drug treatment, is the type of cognition most relevant to psychopharmacology. Intellectual impairments as measured by IQ are not particularly amenable to improvement with drug treatment and, other than with schizophrenia, are not generally associated with psychiatric disorders treated in psychopharmacology. On the other hand, “problems concentrating” and “difficulty paying attention” are seen in many psychiatric disorders and are treatable in a range of conditions, including mood disorders (Chapter 6), anxiety disorders (Chapter 8), schizophrenia and psychotic disorders (Chapter 4), ADHD (Chapter 11), sleep disorders (Chapter 10), and beyond. Such cognitive symptoms are a great example of a domain of psychopathology that cuts across many, many psychiatric disorders and implies that the same circuits and neuronal networks are impaired across all these various disorders. It also implies that the same treatments may work to improve cognition across all these various disorders. “Memory difficulties” are the hallmark of dementia and discussed in Chapter 12. “Memory difficulties” in mood disorders are discussed in Chapter 6 and may be a component of chronic depression and PTSD, when loss of synapses and neurons in a major node in the neuronal network of memory, namely the hippocampus, occurs. If early loss of neurotrophic factors in mood disorders hypothetically causes potentially reversible loss of synapses, it is important to treat cognitive symptoms in depression soon after they emerge so

effective treatments for depression can trigger the release of growth factors and restore synaptogenesis (Figures 6-27 through 6-31), before neurons are lost and the changes become irreversible. Thus, recognizing and targeting cognitive symptoms is becoming more important as new treatments emerge. But how can we recognize and monitor cognitive symptoms in psychopharmacology? A simple if

vortioxetine 5HT1A 5HT1B 5HT1D SERT 5HT3 5HT7 Figure 7-49 Vortioxetine. Vortioxetine is a serotonin reuptake inhibitor and also has actions at several serotonin receptors, including 5HT1A, 5HT1B, 5HT1D, 5HT3, and 5HT7. somewhat whimsical way to categorize cognitive dysfunction and to understand the role of improving individual domains of cognition applicable to psychopharmacology is illustrated in Figure 7-50 as the “Fab Four” of cognition. Remember the original Fab Four, the Beatles? Each musician can represent one of the Fab Four of cognition as well. John, arguably the leader, wanted all the attention, so he represents “attention,” which some also refer to as concentration. Paul, perhaps the brains of the operation and the writer of many of the songs, is “executive function,” also called “problem solving.” The quiet culture carrier of the group, George, represents memory, of which there are many kinds, short-term, long-term, verbal, and more. And finally, the drummer, Ringo, represents processing speed, or pace. You can imagine if any of these four is out of synch with the other three, the music would be a disaster. All four can potentially be compromised in psychiatric disorders. It turns out that for depression, a test that measures a bit of all these dimensions of cognition, but arguably most prominently measures processing speed, is the DSST (digital symbol substitution test). When processing speed is slowed, just like an offbeat drummer in a band, overall cognitive functioning can also feel like a disaster for a depressed patient, lagging in cognitive performance, with mental effort now becoming exhausting and work productivity greatly reduced, all causing great frustration. This simple, quick DSST can be useful in Chapter 7: Treatments for Mood Disorders Figure 7-50 The “Fab Four” of cognition. Cognition is not a single, simple brain function. Rather, there are four major cognitive domains, represented here by the four members of the Beatles: attention or concentration (John), executive function or problem solving (Paul), memory (George), and processing speed (Ringo). All four domains work in concert to keep cognition playing at its best; if any one of these domains dysfunctions, then cognitive impairment can occur. calibrating the objective decline in cognitive performance of patients with subjective cognitive complaints, and in tracking their improvement on treatment. Vortioxetine improves cognition better than other antidepressants in unipolar major depression, as demonstrated by superior performance on the DSST measuring processing speed. How does vortioxetine work as an antidepressant and specifically how does it exert its superior pro-cognitive effects? SERT Inhibition and 5HT1A Agonism To begin, vortioxetine is a SERT inhibitor and a 5HT1A agonist, thus combining the actions already discussed for SSRIs (Figures 7-10 through 7-15) and for combining SERT inhibition with 5HT1A agonists (see Chapter 5 and Figures 7-23 through 7-27). These mechanisms alone are sufficient for antidepressant action since they raise both serotonin levels (SERT inhibition) and the pro317

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-51 SERT inhibition and 5HT1B/D presynaptic antagonism. (A) 5HT1B/D autoreceptors and serotonin transporters (SERTs) are both present on the axon terminal of a serotonin (5HT) neuron. (B) When SERT is inhibited, synaptic availability of serotonin is increased. However, serotonin binding at the 5HT1B/D receptor prevents further serotonin release. (C) When both SERTs and the 5HT1B/D receptors are blocked, increased synaptic serotonin via SERT inhibition is combined with ongoing serotonin release via 5HT1B/D antagonism,

further increasing the availability of serotonin in the synapse. 5HT neuron A SERT SSRI B C 5HT1B/D antagonist 5HT1B/D axon terminal autoreceptor cognitive neurotransmitter dopamine, acetylcholine, and norepinephrine levels (5HT1A agonism) (see also discussion in Chapter 4, Figure 4-44). SERT Inhibition and 5HT1B/D Presynaptic Antagonism An additional receptor action that theoretically raises serotonin levels even further than by SERT inhibition alone is inhibition of the 5HT1B/D presynaptic autoreceptor (Figure 7-51). That is, when SERT is inhibited, the amount of synaptic serotonin that accumulates is blunted because the build-up of serotonin stimulates presynaptic 5HT1B/D autoreceptors, and this turns off further serotonin release (compare Figure 7-51A and B). However, when 5HT1B/D presynaptic autoreceptors are simultaneously inhibited, negative feedback to serotonin release cannot occur, so serotonin release increases even more (Figure 7-51C). 5HT1B Partial Agonism/Antagonism at Heteroreceptors Another putative mechanism of antidepressant and pro-cognitive actions of vortioxetine is antagonist/partial agonist actions on 5HT1B receptors located on presynaptic nerve terminals of acetylcholine, dopamine, histamine, and norepinephrine neurons in the prefrontal cortex. These receptors were discussed earlier in Chapter 4 and illustrated in Figure 4-45, showing how serotonin acting at these receptors inhibits the release of acetylcholine, histamine, dopamine, and norepinephrine. These receptors are shown again in Figure 7-52A and when they are blocked by a 5HT1B partial agonist/antagonist, this enhances the release of the antidepressant and procognitive neurotransmitters dopamine, norepinephrine, histamine, and acetylcholine (Figure 7-52B). SERT Inhibition and 5HT3 Antagonism Another mechanism whereby 5HT3 antagonists enhance the release of the pro-cognitive neurotransmitters acetylcholine, dopamine, and norepinephrine is illustrated in the earlier discussion of 5HT3- antagonism (Figure 7-43) and is one of the most potent of vortioxetine’s several pharmacological actions. SERT Inhibition and 5HT7 Antagonism Serotonin inhibits its own release by actions at 5HT7 receptors (compare Figures 7-53A and 7-53B). Thus, antagonism at 5HT7 receptors enhances serotonin release, especially in the presence of SERT inhibition (Figure 7-53C). Blocking 5HT7 receptors on GABA neurons in the brainstem raphe prevents the downstream inhibition of serotonin release by GABA, especially in the presence of SERT inhibition, and leads instead to increased downstream release of serotonin (Figure 7-53C). 5HT7 receptors also regulate glutamate release downstream in the prefrontal cortex (Figure 7-54A). Blocking these 5HT7 receptors on GABA interneurons enhances the release of glutamate and of downstream monoamine neurotransmitters (compare Figures 7-54A and 7-54B), which may have both antidepressant and pro-cognitive actions. Indeed, in experimental animals, selective 5HT7 antagonists do have pro-cognitive and antidepressant actions. Also, numerous agents with

5HT1B Heteroreceptor Regulation of NE, DA, HA, and ACh in Prefrontal Cortex Baseline Neurotransmitter Release 5HT 1B Raphe NE 1B DA 1B HA 1B ACh A ACh HA BF TMN 5HT1B Antagonist/Partial Agonist Enhances Neurotransmitter Release 5HT 1B 1B 1B 5HT1B antagonist/ partial agonist Raphe 1B 1B 1B 5HT1B antagonist/ partial agonist 1B 1B 1B 5HT1B antagonist/ partial agonist 1B 1B 1B 5HT1B antagonist/ partial agonist BF = Basal Forebrain TMN = Tuberomammillary Nucleus VTA = Ventral Tegmental Area LC = Locus Coeruleus ACh HA BF TMN B 5HT7 antagonism are effective drugs for depression and possibly for improving cognition, including not only vortioxetine, but also trazodone (Figures 7-44 and 7-45), quetiapine, brexpiprazole, aripiprazole, and lurasidone (see Chapter 5 and Figure 5-39). Chapter 7: Treatments for Mood Disorders Figure 7-52 5HT1B heteroreceptors regulate neurotransmitter release. (A) 5HT1B receptors on the presynaptic nerve terminals of norepinephrine (NE), dopamine (DA), acetylcholine (ACh), and histamine (HA) neurons can theoretically regulate the release of these

neurotransmitters. Serotonin (5HT) acting at these receptors would be inhibitory. (B) Antagonism or partial agonism of 5HT1B heteroreceptors on ACh, HA, DA, and NE neurons would prevent serotonin from exerting its inhibitory effects, thus potentially increasing the release of these neurotransmitters. Prefrontal Cortex DA VTA NE LC Prefrontal Cortex DA VTA NE LC Putting it all together, vortioxetine's pharmacological mechanism of action is multimodal, with numerous synergistic mechanisms not only leading to the release of serotonin and to potentiating the release of serotonin (i.e., via SERT, 5HT1B/D presynaptic, and 5HT7 blockade), but 319

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Baseline Serotonin Release baseline 5HT release PFC 5HT7 receptor GABA neuron 5HT neuron raphe also leading to the release of four further antidepressant and pro-cognitive neurotransmitters, namely dopamine, norepinephrine, acetylcholine, and histamine (i.e., via 5HT1A agonism, 5HT1B heteroreceptor partial agonism/ antagonism, and 5HT3 antagonism). This unique combination of mechanisms may account for the unique pro-cognitive actions of vortioxetine in unipolar major depression. Figure 7-53A 5HT7 receptors regulate serotonin release, part 1. 5HT7 receptors are located on GABA interneurons in the raphe nucleus. At baseline, when these receptors are not bound, serotonin is released into the prefrontal cortex. overactivation Neuroactive Steroids Another rapid-onset mood treatment is the neuroactive steroid brexanolone, a cyclodextrin-based intravenous formulation of the naturally occurring neuroactive steroid allopregnanolone (Figure 7-55). Administered by a 60-hour intravenous infusion for postpartum depression, brexanolone has a rapid-onset and sustained antidepressant effect. As briefly mentioned in Chapter 6,

Chapter 7: Treatments for Mood Disorders raphe PFC 5HT7 receptor reduced 5HT release overactivation Stimulation of 5HT7 Receptors in the Raphe Reduces Serotonin Release GABA neuron 5HT neuron 5HT7 Inhibits Serotonin Release Figure 7-53B 5HT7 receptors regulate serotonin release, part 2. When serotonin binds to 5HT7 receptors on GABA interneurons in the raphe nucleus, this stimulates GABA release. GABA in turn inhibits serotonin release in the prefrontal cortex. pregnant women have high circulating and presumably brain levels of naturally occurring allopregnanolone. After delivery of the baby, there is a precipitous decline in circulating and presumably brain levels of neuroactive steroids, hypothetically triggering the sudden onset of a major depressive episode in vulnerable women. Rapidly restoring neuroactive steroid levels over a 60-hour period of continuous intravenous infusion with brexanolone rapidly reverses depression, and the 60-hour duration of administration seems to provide the time necessary for postpartum patients to accommodate to their lower levels of neuroactive steroids without relapsing, following the infusion. Neuroactive steroids bind to GABAA receptors at a specific allosteric site called the neuroactive steroid site, which enhances the inhibitory action of GABA at GABAA receptors (Figure 7-56; see also discussion in Chapter 6 and Figures 6-20 and 6-21). Neuroactive steroids target the benzodiazepine-sensitive GABAA receptors, just like benzodiazepines (Figure 7-56A) but also the benzodiazepine-insensitive GABAA receptors, unlike benzodiazepines (Figure 7-56B).

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY raphe PFC 5HT7 antagonist increased 5HT release overactivation GABA neuron 5HT neuron 5HT7 Antagonist Enhances Serotonin Release Figure 7-53C 5HT7 receptors regulate serotonin release, part 3. Antagonism at 5HT7 receptors on GABA interneurons in the raphe nucleus turns off GABA release. This prevents the downstream inhibition of serotonin release by GABA, thus increasing serotonin in the prefrontal cortex. Certain general anesthetics (e.g., propofol, etomidate, alphaxolone, alfadalone) also bind at the same sites as

neuroactive steroids, but are dosed much higher. Since benzodiazepines do not have antidepressant actions, it is the targeting of the benzodiazepine-insensitive GABAA receptors (Figure 7-56B) that is thought to be the primary mechanism of antidepressant action of neuroactive steroids. The benzodiazepine-insensitive GABAA receptors are extrasynaptic and mediate tonic inhibition (see discussion in Chapter 6 and Figure 6-20). The way in which engaging their allosteric neuroactive steroid sites results in a rapid and possibly enduring treatment for major depression is unknown. Hints as to why boosting GABA action may be effective for a novel approach to the treatment of depression come from observations that GABA levels are reduced in the plasma, spinal fluid, and brains of depressed patients; GABA interneurons are reduced in brains of depressed patients; and mRNA levels for the specific GABAA receptor subunits that encode the benzodiazepine-insensitive GABAA receptor subtypes are also deficient in brains of depressed patients who died by suicide. Perhaps neuroactive steroids compensate for these GABA-related defects and this is how they mediate their rapid-onset antidepressant actions. SAGE-217 (Figure 7-57) is a synthetic orally active allopregnanolone analogue in clinical testing as a rapidonset antidepressant for major depressive disorder, with some promising preliminary results.

Baseline Glutamate Release pyramidal neuron GABA neuron 5HT7 receptor PFC 5HT neuron raphe TREATMENT RESISTANCE IN UNIPOLAR DEPRESSION Choosing Treatment for Treatment Resistance in Depression on the Basis of Genetic Testing Genetic testing has the potential of assisting the selection of psychotropic drug treatment for depression, especially when several first-line treatments have failed to work or to be tolerated. Genotyping has already entered other specialties in medicine, and is poised to enter mental health practice. In the not-too-distant future, experts foresee that most patients will have their entire genomes entered as part of their permanent electronic medical Chapter 7: Treatments for Mood Disorders Figure 7-54A 5HT7 receptors regulate glutamate release, part 1. 5HT7 receptors are located on GABA interneurons in the prefrontal cortex, which themselves synapse with glutamate neurons. At baseline, when these receptors are not bound, glutamate is released. baseline glutamate release overactivation records. In the meantime, it is possible to obtain from various laboratories genetic variants for a number of genes that regulate drug metabolism (pharmacokinetic genes) and that hypothetically regulate efficacy and side effects of drugs in depression (pharmacodynamic genes). For example, several genetic forms of numerous cytochrome P450 (CYP450) drug metabolizing enzymes can be obtained to predict high or low levels of drug, and therefore lack of efficacy (low drug levels) or side effects (high drug levels). These findings can also be coupled with phenotyping, namely obtaining the actual plasma drug level itself. CYP450 genotypes and the actual plasma drug levels together can thus potentially help explain side effects and lack of therapeutic effects in some patients. 323

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY raphe PFC overactivation enhanced glutamate release 5HT7 Antagonist Enhances Glutamate Release pyramidal neuron GABA neuron 5HT neuron 5HT7 antagonist Figure 7-54B 5HT7 receptors regulate glutamate release, part 2. Antagonism at 5HT7 receptors on GABA interneurons in the prefrontal cortex turns off GABA release. This prevents inhibition of glutamate release by GABA, thus increasing glutamate downstream. Figure 7-55 Brexanolone. Brexanolone is a cyclodextrin-based intravenous formulation of the naturally occurring neuroactive steroid allopregnanolone. HO OH OH OH OH CH OH CH OH CH OH OH OH OH OH H H H H O dextrin allopregnanolone O O O O O

Chapter 7: Treatments for Mood Disorders Figure 7-56 Neuroactive steroid binding site on GABAA neurons. Neuroactive steroids bind to GABAA receptors at a specific allosteric site called the neuroactive steroid site to enhance the inhibitory action of GABA at these receptors. Neuroactive steroids bind to both benzodiazepine-sensitive (A) and benzodiazepine-insensitive (B) GABAA receptors. = GABA A B = benzodiazepine = neuroactive steroid ß ß GABA binding site benzodiazepine and neuroactive steroid binding site chloride channel α α γ ß ß GABA binding site neuroactive steroid binding site chloride channel α4,6

α4,6 Figure 7-57 SAGE-217. SAGE-217 is a synthetic orally active allopregnanolone analogue in clinical testing as a rapid onset antidepressant for major depressive disorder. Neuroactive Steroid allopregnanolone analogue SAGE-217 whether the patient is “biased” towards responding or not, tolerating or not, and, along with past treatment response, help the clinician make a future treatment recommendation that has a higher chance of success but is not guaranteed to be effective and tolerated. Some call this process the “weight of the evidence” and others “equipoise,” where the genetic information will enrich the prescribing decision, but not necessarily dictate a single compelling choice. Genetic testing makes the prescriber think about, and develop feasible neurobiologically based hypotheses for, the next choices in treatment, rather than mere random selection from amongst treatments that have not yet been attempted. Augmenting Strategies for Unipolar Depression As discussed above and illustrated in Figures 7-4 and 7-6, there are diminishing returns of efficacy for unipolar depression, the more drugs for depression that are tried. This has led to earlier use of antidepressant combinations for patients who do not respond well to a single agent, in an attempt to add together synergistic mechanisms that could help the patient attain remission. Serotonin/Dopamine Antagonists/Partial Agonists as Augmenting Agents for Treatment-Resistant Unipolar Depression Serotonin/dopamine blocking agents originally developed for psychosis are now some of the most common adjunctive treatments to SSRIs/SNRIs in patients with unipolar depression who fail to respond adequately to one Treatment responses are not “all or none” phenomena, and genetic markers in psychopharmacology will, in all likelihood, explain a greater or lesser likelihood of response, nonresponse, or side effects, but will not tell a clinician with certainty what drug to prescribe for a specific individual to guarantee a clinical response or avoid a side effect. So far, and for the foreseeable future, in the practice of psychopharmacology, the information obtained from pharmacogenomics will likely tell

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Its efficacy as an augmenting agent to SSRIs/SNRIs for depression is likely linked to the combined actions of quetiapine and its active metabolite norquetiapine at both 5HT2C receptors (Figure 7-38) and at the norepinephrine transporter (NET) (Figure 5-34; also described in Chapter 5 and illustrated in Figure 5-45). In addition, quetiapine acts at other candidate receptors for antidepressant efficacy including as an antagonist at 5HT2A (Chapter 5 and Figure 5-17C), 5HT7 (Figure 7-53C) and α2A receptors (Figure 5-35), as well as an agonist at 5HT1A receptors (Chapter 5 and Figure 5-22). All of these receptor actions are hypothetically associated with antidepressant efficacy and, added together, could make a theoretically powerful synergy of antidepressant mechanisms (Table 7-1). However, quetiapine can cause a great deal of sedation and moderate weight gain and metabolic disturbance due to its other receptor actions. Quetiapine is also approved for bipolar depression and discussed in the section on bipolar depression below. Aripiprazole This D2/5HT1A partial agonist (Chapter 5 and Figure 5-56) is approved for schizophrenia, acute bipolar mania, and bipolar maintenance and is one of the most extensively prescribed augmenting agents to SSRIs/ SNRIs in unipolar major

depression (in the US) (Table 7-1). It likely acts in schizophrenia and bipolar mania as a D2 partial agonist, whereas its prominent 5HT1A partial agonist actions (Chapter 5 and Figure 5-22) likely contribute to its antidepressant actions. Secondary properties with potential antidepressant action may also be contributory including D3, 5HT7, 5HT2C, and α2 or more trials of the various first-line monoamine agents discussed so far in this chapter. Olanzapine–Fluoxetine Combination Dopamine 2 (D2) antagonist actions likely account for olanzapine's approval in schizophrenia, bipolar mania, and bipolar maintenance. 5HT2A antagonist actions likely account for some of olanzapine's ability to improve symptoms of depression (5HT2A actions on mood are discussed in Chapter 5 and illustrated in Figure 5-17C). However, the fact that olanzapine works much better for unipolar (or bipolar) depression when combined with fluoxetine suggests that not only are serotonin reuptake blocking properties a component of the antidepressant effect of olanzapine–fluoxetine combination therapy, but also 5HT2C antagonist actions (Figure 7-38). Both olanzapine and fluoxetine are 5HT2C antagonists, and, in combination, the net 5HT2C antagonism is greater than with either drug alone. So, this olanzapine–fluoxetine combination for depression could be considered a potent SERT/5HT2C inhibitor. Although highly efficacious for treatment-resistant unipolar depression (Table 7-1), the combination of olanzapine with fluoxetine is often associated with unacceptable weight gain and metabolic disturbances. Olanzapine–fluoxetine combination is also approved for bipolar depression and is discussed in the section on bipolar depression below. Quetiapine Quetiapine (see Chapter 5 and Figure 5-45) is approved for schizophrenia, acute bipolar mania, and bipolar maintenance, likely due to its D2 antagonist actions. Table 7-1 Serotonin/dopamine blockers for bipolar spectrum Evidence of efficacy in mixed features FDA-approved for bipolar depression FDA-approved for bipolar mania FDA-approved for bipolar maintenance FDA-approved for major depressive disorder Aripiprazole Yes Yes Yes (adjunct) Asenapine Yes, MMX Yes Yes Brexpiprazole Yes (adjunct) Cariprazine Yes, MMX, DMX Yes Yes Lurasidone Yes, DMX* Yes Olanzapine Yes, MMX Yes (with fluoxetine) Yes Yes Yes (with fluoxetine) Quetiapine Yes, MMX Yes Yes Yes Yes (adjunct) Risperidone Yes Yes Ziprasidone Yes, MMX Yes Yes MMX, mania with mixed features; DMX, depression with mixed features. *unipolar and bipolar depression.

Chapter 7: Treatments for Mood Disorders 5-22A), and α1 (Figure 7-58A) binding of brexpiprazole compared to aripiprazole (compare the binding strips of aripiprazole in Figure 5-56 and brexpiprazole in Figure 5-57). As can be seen in these figures, brexpiprazole also has more potent α2 antagonist, 5HT7 antagonist, and D3 partial agonist binding than aripiprazole. These various differences in receptor binding profiles could theoretically contribute to different mechanisms of therapeutic action and side effects for brexpiprazole compared to aripiprazole. Alpha-1 antagonist actions have been discussed in Chapter 5 and illustrated in Figure 5-13B showing how α1 antagonism, particularly in the thalamus, could contribute to sedation when coupled with simultaneous blockade of muscarinic cholinergic and histamine receptors in the reticular activating arousal system (Chapter 5, Figures 5-13A and 5-8). However, particularly antagonist actions. Aripiprazole is generally well tolerated with little weight gain but some patients experience akathisia. Aripiprazole is not approved for the treatment of bipolar depression. Brexpiprazole Another D2/5HT1A partial agonist (see Chapter 5 and Figure 5-57) is approved for schizophrenia and also for adjunctive treatment in unipolar depression (Table 7-1). Brexpiprazole is not approved for the treatment of bipolar depression. As mentioned earlier in discussion of brexpiprazole for psychosis in Chapter 5, there is some indication of reduced akathisia with brexpiprazole compared to aripiprazole, but this has not been proven in head-to-head trials. Reduced akathisia would be consistent with the binding profile of enhanced 5HT2A (Chapter 5, Figure 5-17B), 5HT1A (Chapter

5, Figure Figure 7-58 Alpha-1 antagonism and downstream dopamine release. Alpha-1 antagonism can modulate downstream dopamine release via two key pathways. (A) Alpha-1 antagonism decreases glutamatergic output in the substantia nigra (SN), leading to reduced activity of the GABA interneuron and therefore disinhibition of the nigrostriatal dopamine pathway. The increased dopamine release in the motor striatum can reduce motor side effects caused by D2 antagonism because there is more dopamine to compete with the D2 antagonist. (B) Alpha-1 antagonism reduces glutamatergic output in the ventral tegmental area (VTA), leading to reduced activity of the GABA interneuron and therefore disinhibition of the mesocortical dopamine pathway. Increased dopamine release in the prefrontal cortex (PFC) can potentially improve mood and reduce affective and cognitive symptoms. PFC PFC A B (SIGH) VTA SN motor striatum improved mood, affective symptoms, and cognitive symptoms reduction in DIP α1 receptor α1 antagonist α1 receptor α1 antagonist

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY without simultaneous muscarinic and histaminic antagonism, α1 antagonist action in the prefrontal cortex could hypothetically also contribute both to the reduced motor side effects and to the known antidepressant effects seen with potent α1 antagonists, particularly those with simultaneous 5HT2A antagonist properties. Alpha-1 antagonist actions of brexpiprazole could also potentially contribute to its evidence of efficacy for agitation in Alzheimer disease and in PTSD (as augmentation of sertraline). How does this happen and what circuits regulate α1 antagonist action? The answer is that the reader is already familiar with the circuitry to explain the actions of α1 antagonists, since it is the same circuitry already discussed for 5HT2A receptors and illustrated in Chapter 5 in Figures 5-16 and 5-17. It is now known that α1 receptors (illustrated here in Figure 7-58) are colocalized on the same pyramidal neurons with 5HT2A receptors (discussed in Chapter 5 and illustrated in Figures 5-16 and 5-17). Since both α1 receptors and 5HT2A receptors are excitatory and postsynaptic, norepinephrine and serotonin acting together exert a more powerful excitatory control of prefrontal cortex function through their simultaneous action than either neurotransmitter acting alone. Furthermore, the actions of an α1 antagonist would be expected to have the same functional effects as a 5HT2A antagonist, the two actions acting together to have a more powerful downstream inhibitory control of the prefrontal cortex output than blockade of either receptor alone. Figure 7-58A shows the α1 receptors on those specific pyramidal neurons projecting to the substantia nigra (same pyramidal neurons and circuitry as shown in Chapter 5, Figure 5-17B). When this glutamatergic neuron is inhibited by an α1 antagonist, its innervation of the substantia nigra reduces GABA tone there, allowing disinhibition of dopamine release into the motor striatum and reduction of drug-induced parkinsonism (Figure 7-58A; just as shown in Chapter 5 and Figure 5-17B). Thus, drug-induced parkinsonism caused by D2 blockers will be maximally reduced by those D2 blockers that have both 5HT2A and α1 antagonist actions. Indeed, the lowest frequency and severity of drug-induced parkinsonism induced by dopamine blockers is for those that also have robust α1 and 5HT2A antagonist actions, namely, brexpiprazole, quetiapine, clozapine, and iloperidone. Synergy of α1 antagonism with 5HT2A antagonism can theoretically also enhance antidepressant action, this time in the circuit of pyramidal neurons innervating the ventral tegmental area dopamine neurons that project to the prefrontal cortex (Figure 7-58B and Chapter 5, Figure 5-17C). What this means is that α1 antagonists would theoretically have the same effect as 5HT2A antagonists in this circuit, and the two working together would exert a more powerful control of the prefrontal cortex and its downstream projections, to further facilitate dopamine release in the prefrontal cortex and to cause antidepressant action. In fact, this synergy is likely to be an important component of the

mechanism of antidepressant action for those agents that are both α1 and 5HT2A antagonists, including brexpiprazole, quetiapine, and trazodone. The enhancement of dopamine release in the prefrontal cortex by simultaneous α1 and 5HT2A blockade may theoretically contribute as well to improving “top-down” control of agitation in Alzheimer disease and PTSD symptoms, which are seen in ongoing studies of brexpiprazole. Cariprazine Carpirazine (Chapter 5 and Figure 5-58) is a D3/D2/5HT1A partial agonist as well as a 5HT2A/α1/α2 antagonist, approved for the treatment of acute bipolar mania and bipolar depression; it also has evidence of efficacy as an adjunct to SSRI/SNRIs in unipolar depression (Table 7-1). Cariprazine’s antidepressant mechanism of action is discussed below in the section on treating bipolar depression. Ketamine Observations that the intravenous infusion of subanesthetic doses of ketamine could rapidly improve depression in patients inadequately responsive to monoamine-targeting drugs has set forth a bit of a revolution in the treatment of depression. Ketamine is an approved anesthetic but used off-label for treatmentresistant depression. Whereas serotonin/dopamine blockers tend to be used after just one or two failures of an SSRI/SNRI, ketamine tends to be given to patients with multiple failures on various drugs for depression. Intravenous ketamine is a racemic mixture of R- and S-ketamine, each with overlapping binding properties at the NMDA subtype of glutamate receptor, its putative mechanism of antidepressant action, and at the σ1 receptor (Figure 7-59). Actions at other sites, including μ-opioid and other neurotransmitter sites, are proposed but disputed, especially the possibility that ketamine’s antidepressant actions may be linked in some way to μ-opioid as well as NMDA action. Thus, a debate exists as to how ketamine exerts its rapid-onset antidepressant effects, but NMDA antagonism – specifically at the

Chapter 7: Treatments for Mood Disorders Figure 7-59 Ketamine. Ketamine is used off-label and is being studied for its potential therapeutic utility in treatment-resistant depression. Ketamine is an NMDA (N-methyl-D-aspartate) receptor antagonist, with additional weak actions at σ1 receptors, the norepinephrine transporter (NET), μ-opioid receptors, and the serotonin transporter (SERT). Ketamine consists of two enantiomers, R and S. NMDA + + NMDA + + ketamine: R+S ketamine NMDA σ NMDA σ σ σ S-ketamine R-ketamine open-channel phencyclidine (PCP) site (see discussion in Chapter 4 and Figure 4-30) – is the leading hypothesized target for explaining ketamine’s antidepressant effects. What is unique about ketamine infusions is the rapid, almost immediate onset of antidepressant effects, sometimes accompanied by specific antisuicidal ideation effects, in patients who seem to have “nonmonoaminergic” depressions since they have failed numerous standard monoamine-targeted antidepressant therapies. Unfortunately, the antidepressant effects of ketamine are usually not long lasting, but generally fade over a few days. In some cases, the antidepressant effects can be re-triggered by repeated infusions over time, or enhanced by monoaminergic antidepressant treatments following infusions. Most interesting perhaps is the possibility that ketamine causes immediate improvement in neuronal plasticity as its downstream mechanism of immediately improving depression. Loss of neurotrophic factors in depression is discussed in Chapter 6 and illustrated in Figures 6-27 through 6-33). Recall that the neurotrophic hypothesis of depression and antidepressant response is based on evidence that deficiencies in neurotrophic factors such as BDNF (brain-derived neurotrophic factor) and possibly other growth factors such as VEGF (vascular endothelial growth factor) occur with chronic stress and major depression and that when monoaminergic drugs for depression are effective, they restore these growth factors, but with a delay of weeks after drug administration. On the other hand, when monoaminergic drugs for depression are not effective, it is assumed that for unknown reasons monoamines cannot restore the necessary growth factors. Loss of BDNF and VEGF are both linked

to neuronal atrophy in brain regions such as the prefrontal cortex and hippocampus in chronic stress models in animals as well as in unipolar major depressive disorder. Chronic stress and depression are also thought to decrease the receptors for BDNF and VEGF, namely TRKB (tyrosine kinase 2) and FLK1 (fetal liver kinase 1), respectively. Ketamine increases both of these growth factors. So, how does ketamine induce its rapid antidepressant response and rapid reversal of synaptic atrophy in depression? This is thought to occur because ketamine

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Glu Glu NMDA receptor and synapse blocked by subanesthetic infusion of ketamine burst of Glu release from upstream NMDA antagonism causes an immediate burst of downstream glutamate release after blocking NMDA receptors (discussed in Chapter 4 and illustrated in Figure 4-33; see also Figure 7-60). Ketamine's actions at NMDA receptors are not unlike what is hypothesized to occur due to neurodevelopmental abnormalities at NMDA synapses in schizophrenia (also discussed in Chapter 4 and illustrated in Figures 4-29B and 4-31 through 4-33). This is not surprising given that ketamine can produce a schizophrenia-like syndrome in humans especially at high doses and acute drug administration (Figure 4-33). However, when infused over time and at subanesthetic doses in the study of depressed patients, ketamine does not induce psychosis, but is thought to produce downstream release in glutamate (Figure 7-60). Glutamate that is released in this burst stimulates Figure 7-60 Mechanism of action of ketamine. Shown here are two cortical glutamatergic pyramidal neurons and a GABAergic interneuron. (1) If an Nmethyl-D-aspartate (NMDA) receptor on a GABAergic interneuron is blocked by ketamine, this prevents the excitatory actions of glutamate (Glu) there. Thus, the GABA neuron is inactivated and does not release GABA (indicated by the dotted outline of the neuron). (2) GABA binding at the second cortical glutamatergic pyramidal neuron normally inhibits glutamate release; thus, the absence of GABA there means that the neuron is disinhibited and glutamate release is increased. AMPA receptors while ketamine is blocking NMDA receptors (Figures 7-61 and 7-62). One hypothesis for why ketamine has antidepressant actions proposes that this stimulation of AMPA receptors first activates the ERK, AKT signal transduction cascade (Figures 7-61A). This then triggers the mTOR (mammalian target of rapamycin) pathway (Figures 7-61) and that causes the expression of synaptic proteins, leading to an increased density of dendritic spines (Figures 7-61B). Dendritic spine proliferation indicating new synaptogenesis can be seen within minutes to hours after ketamine is administered in animals. Hypothetically, it is this increase in dendritic spines and synaptogenesis that causes the rapid-onset antidepressant effect. Another hypothesis for why ketamine has antidepressant actions proposes that the stimulation of AMPA receptors from the burst

burst of Glu release from upstream NMDA antagonism Glu AMPA receptor stimulated by Glu NMDA receptor blocked by ketamine ERK, AKT mTOR A Glu AMPA receptor NMDA receptor blocked by ketamine ERK, AKT mTOR B of glutamate release (Figure 7-62A) activates another signal transduction pathway, namely voltage-sensitive calcium channels, which allow calcium influx that in turn activates BDNF and VEGF release to induce synaptic formation (Figure 7-62B). Thus, ketamine hypothetically reverses the atrophy caused by depression, and does this within minutes. Chapter 7: Treatments for Mood Disorders Figure 7-61 Ketamine, AMPA receptors, and mTOR. Glutamate activity heavily modulates synaptic potentiation; this is specifically modulated through NMDA

(N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4isoxazole-propionic acid) receptors. Ketamine is an NMDA receptor antagonist; however, its rapid antidepressant effects may also be related to indirect effects on AMPA receptor signaling. (A) One hypothesis is that blockade of the NMDA receptor leads to rapid activation of AMPA, which triggers the ERK, AKT signal transduction cascade, which then triggers the mammalian target of rapamycin (mTOR) pathway. (B) This in turn would lead to rapid AMPAmediated synaptic potentiation and increase in dendritic spine formation. Traditional antidepressants also cause synaptic potentiation; however, they do so via downstream changes in intracellular signaling. This may therefore explain the difference in onset of antidepressant action between ketamine and traditional antidepressants. dendritic spine formation dendritic spine formation Esketamine The S enantiomer of ketamine is approved for treatmentresistant depression in an intranasal formulation for administration, and is called esketamine (Figure 7-63). The exact pharmacology of R- versus S-ketamine and their active metabolites is still being determined in terms of neurotrophic actions. However, esketamine is indeed 331

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY TRKB FLK1 vesicle with VEGF vesicle with BDNF Ca++ Glu AMPA receptor VSCC NMDA receptor blocked by ketamine A BDNF VEGF PLC AKT B active as an acute rapid-onset antidepressant, and it is administered intranasally and rapidly, so that longer intravenous infusions are not necessary. After twiceweekly initiation, esketamine can be given intranasally in weekly or biweekly dosing as an augmenting agent to standard drugs for depression. A long-term study for up to a year of esketamine nasal spray plus a switch to an oral monoamine antidepressant not previously tried, showed sustained improvements in depression and acceptable safety. Other Drug Combinations for Treatment-Resistant Depression Other options to augment monoamine treatments for unipolar depression include agents that do not have robust antidepressant actions as monotherapies but can improve the action of the monoamine treatments Figure 7-62 Ketamine, AMPA receptors, and BDNF/VEGF release. Glutamate activity heavily modulates synaptic potentiation; this is specifically modulated through NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5methyl-4-isoxazole-propionic acid) receptors. Ketamine is an NMDA receptor antagonist; however, its rapid antidepressant effects may also be related to indirect effects on AMPA receptor signaling. (A) A second hypothesis is that blockade of the NMDA receptor leads to rapid activation of AMPA, which activates voltage-sensitive calcium channels (VSCCs) to allow calcium influx. (B) This in turn would lead to activation of brainderived neurotrophic factor (BDNF) and VEGF (vascular endothelial growth factor) release, which bind to TRKB and FLK1 receptors, respectively, triggering cascades that induce dendritic spine formation. /PI3K dendritic spine formation (e.g., lithium, buspirone, and thyroid), as well as the very popular and often effective strategy of combining two monoamine drugs, each approved for unipolar depression, to create pharmacological synergy. However, none of these strategies are specifically approved. Lithium Lithium is discussed below as a treatment for mania, but has been used as well for unipolar depressed patients who fail to respond to treatment. Lithium augmentation of monoamine reuptake inhibitors, particularly the classic tricyclic antidepressants also discussed below, has been used in the past to boost treatment response in unipolar depression. As augmentation for treatment-resistant unipolar depression, lithium is administered in doses lower than those used for mania, but it has fallen out of favor in recent years.

esketamine NMDA σ S-ketamine σ NMDA + + Figure 7-63 Esketamine. The R and S enantiomers of ketamine are mirror images of each other; the exact pharmacology of the R and S enantiomers and

their active metabolites is still being determined. The S enantiomer of ketamine has been developed and marketed as esketamine. Buspirone Buspirone is a 5HT1A partial agonist, so putting it together with an SSRI/SNRI is very much similar to the use of vilazodone (Figure 7-22 through Figure 7-27) or vortioxetine (Figure 7-49) discussed above. Indeed, most of the serotonin/dopamine agents used to augment monoamine antidepressants have 5HT1A properties (e.g., quetiapine, aripiprazole, brexpiprazole, and cariprazine). Administering drugs that have 5HT1A agonist actions is a favored approach for augmenting SSRI/SNRIs, but using buspirone for this is less common today than using other agents with 5HT1A properties. Thyroid Hormones Thyroid hormones act by binding to nuclear ligand receptors to form a nuclear ligand-activated transcription factor. Abnormalities in thyroid hormone levels have long been associated with depression, and various forms and doses of thyroid hormones have for many years been utilized as augmenting agents to drugs for depression either to boost their efficacy in patients with inadequate response or to speed up their onset of action. Thyroid's Chapter 7: Treatments for Mood Disorders known abilities to regulate neuronal organization, arborization, and synapse formation may have the downstream consequence of boosting monoamine neurotransmitters, and this may account for how thyroid hormones enhance antidepressant action in some patients. Augmentation of treatments for either unipolar or bipolar depression with thyroid hormones has also fallen out of favor in recent years. Triple-Action Combo: SSRI/SNRI + NDRI If boosting one neurotransmitter is good, and two is better, maybe three boosted neurotransmitters is best (Figures 7-64). Triple action (i.e, serotonin, dopamine, and norepinephrine) drugs for depression therapy with modulation of all three monoamines would be predicted to occur by combining either an SSRI with an NDRI or combining an SNRI with an NDRI, providing even more noradrenergic and dopaminergic action (Figure 7-64). These are perhaps some of the most popular combinations of two drugs for depression utilized in the US. California Rocket Fuel: SNRI plus Mirtazapine This potentially powerful combination exploits the pharmacological synergy attained by adding the enhanced serotonin and norepinephrine release from inhibition of both serotonin and norepinephrine reuptake by an SNRI to the disinhibition of both serotonin and norepinephrine release by the α2 antagonist actions of mirtazapine (Figure 7-65). It is even possible that additional pro-dopaminergic actions result from the combination of norepinephrine reuptake blockade in the prefrontal cortex due to SNRIs with 5HT2C actions of mirtazapine disinhibiting dopamine release. This combination can provide very powerful antidepressant action for some patients with unipolar major depressive episodes. Arousal Combos The frequent complaints of residual fatigue; loss of energy, motivation, and sex drive; and problems concentrating/problems with alertness may be approached by combining either a stimulant (dopamine transport inhibitor or DAT inhibitor) with an SNRI, or modafinil (another DAT inhibitor) with an SNRI (Figure 7-66), to recruit triple monoamine action and especially enhancement of dopamine. Second-Line Monotherapies Used for TreatmentResistant Depression Tricyclic Antidepressants The tricyclic antidepressants (TCAs) (Table 7-2; Figure 7-67) were so-named because their chemical 333

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY = SSRI = NDRI A B SNRI SSRI + NDRI Triple-Action Combos DA 5HT NE single boost single boost single boost = SNRI = NDRI SNRI + NDRI DA 5HT NE single boost double boost single boost SERT SSRI NDRI NET NDRI DAT SERT SNRI NDRI NET NDRI DAT Figure 7-64 Triple-action combo: SSRI/SNRI plus NDRI. (A) Selective serotonin reuptake inhibitor (SSRI) plus a norepinephrine– dopamine reuptake inhibitor (NDRI) leads to a single boost for serotonin (5HT), norepinephrine (NE), and dopamine (DA). (B) Serotonin– norepinephrine reuptake inhibitor (SNRI) plus a norepinephrine–dopamine reuptake inhibitor (NDRI) leads to a

single boost for serotonin (5HT), a double boost for norepinephrine (NE), and a single boost for dopamine (DA). Figure 7-65 California rocket fuel: SNRI plus mirtazapine. Combining a serotonin–norepinephrine reuptake inhibitor (SNRI) with mirtazapine is a combination that has a great degree of theoretical synergy: serotonin (5HT) is quadruple-boosted (with reuptake blockade, α2 antagonism, 5HT2A antagonism, and 5HT2C antagonism), norepinephrine (NE) is quadruple-boosted (with reuptake blockade, α2 antagonism, 5HT2A antagonism, and 5HT2C antagonism), and there may even be a double boost of dopamine (DA) (with 5HT2A and 5HT2C antagonism). mirtazapine mirtazapine mirtazapine California Rocket Fuel SNRI = SNRI = mirtazapine SNRI + mirtazapine DA 5HT NE quadruple boost quadruple boost double boost SERT SNRI NET 5HT 2A 5HT 2A 5HT 2C 5HT 2C 5HT 2A 5HT 2C α2 α2

Chapter 7: Treatments for Mood Disorders Figure 7-66 Arousal combo: SNRI plus stimulant/modafinil. (A) Serotonin (5HT) and dopamine (DA) are single-boosted and norepinephrine (NE) is double-boosted when a serotonin–norepinephrine reuptake inhibitor (SNRI) is combined with a stimulant. (B) Serotonin (5HT) and norepinephrine (NE) are single-boosted by the serotonin–norepinephrine reuptake inhibitor (SNRI) while dopamine (DA) is single-boosted by modafinil. stimulant stimulant modafinil Arousal Combos B SNRI = SNRI = modafinil SNRI + modafinil DA 5HT NE single boost single boost single boost SERT SNRI NET DAT A SNRI = SNRI = stimulant SNRI + stimulant DA 5HT NE single boost double boost single boost SERT SNRI NET DAT Table 7-2 Some tricyclic antidepressants still in use Generic name Trade name Clomipramine Anafranil Imipramine Tofranil Amitriptyline Elavil; Endep; Tryptizol; Laroxyl Nortriptyline Pamelor; Aventyl Protriptyline Vivactil Maprotiline Ludiomil Amoxapine Asendin Doxepin Sinequan; Adapin Desipramine Norpramin; Pertofran Trimipramine Surmontil Dothiepin Prothiaden Lofepramine Deprimyl; Gamanil Tianeptine Coaxil; Stablon structure contains three rings. The TCAs were synthesized about the same time that other threeringed phenothiazine molecules were shown to be effective tranquilizers for schizophrenia (i.e., the early D2 antagonist drugs such as chlorpromazine) but were a disappointment when tested as drugs for psychosis. However, during testing for schizophrenia, they were serendipitously discovered to be effective in unipolar depression. Tricyclic antidepressants are not merely drugs for depression since one of them (clomipramine) has anti-obsessive–compulsive disorder; many of them have anti-panic effects at antidepressant doses and efficacy for neuropathic and low back pain at low doses. Long after their antidepressant properties were observed, the TCAs were discovered to block the reuptake pumps for norepinephrine (i.e., NET), or for both norepinephrine and serotonin (i.e., SERT) (see Figure 7-67A). Some tricyclics have equal or greater potency for SERT inhibition (e.g., clomipramine); others are more selective for NET inhibition (e.g., desipramine, maprotiline,

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY TCA sodium channel blocker H1 H1 Na+ α1 SERT NET M1 A sodium channel blocker H1 H1 Na+ α1 NET M1 B sodium channel blocker H1 H1 Na+ α1 SERT 5HT2A 5HT2C NET M1 C Figure 7-67 Icons of tricyclic antidepressants (TCAs). All tricyclic antidepressants block reuptake of norepinephrine and are antagonists at histamine 1 (H1), α1-adrenergic, and muscarinic cholinergic receptors; they also block voltagesensitive sodium channels (A, B, and C). Some TCAs are also potent inhibitors of the serotonin reuptake pump (A, C), and some may additionally be antagonists at serotonin 2A and 2C receptors (C). nortriptyline, protriptyline) (Figure 7-67B). Most, however, block both serotonin and norepinephrine reuptake to some extent (Figure 7-67A). In addition, some TCAs have antagonist actions at 5HT2A and 5HT2C receptors, which could contribute to the therapeutic profile of those tricyclics that have such

pharmacological actions (Figure 7-67C). The major limitation to the TCAs has never been their efficacy: these are quite effective agents. The problem with drugs in this class is the fact that all of them share at least four other unwanted pharmacological actions, namely, blockade of muscarinic cholinergic receptors, H1 histamine receptors, α1-adrenergic receptors, and voltagesensitive sodium channels (Figure 7-67). As already discussed, blockade of H1 receptors causes sedation and may cause weight gain (see Chapter 5 and Figure 5-13A). Blockade of muscarinic cholinergic receptors, also known as anticholinergic actions, causes dry mouth, blurred vision, urinary retention, and constipation (Figure 5-8). Blockade of α1-adrenergic receptors may be therapeutic but also causes orthostatic hypotension and dizziness (Figure 5-13B). Tricyclic antidepressants also weakly block voltage-sensitive sodium channels in the heart and brain at therapeutic doses; in overdose, this action is thought to be the cause of coma and seizures due to central nervous system actions, and cardiac arrhythmias and cardiac arrest and death due to peripheral cardiac actions (Figure 7-68). The lethal dose of a TCA is only about a 30-day supply of drug. For this reason, it has been said that each time you are giving the patient a 1-month's prescription for a TCA, you are handing them a loaded gun. Obviously, this is often not a good idea in the treatment of a disorder associated with so much suicide; thus, TCAs have largely fallen out of favor except for patients who fail to respond to the various first-line drugs for depression discussed up to this point in this chapter. Monoamine Oxidase Inhibitors (MAOIs) The first clinically effective drugs for depression ever discovered were inhibitors of the enzyme monoamine oxidase (MAO). They were found by accident when an anti-tuberculosis drug was observed to help depression that coexisted in some of the patients who had tuberculosis. This anti-tuberculosis drug, iproniazid, was eventually found to work in depression by inhibiting the enzyme MAO. However, inhibition of MAO was unrelated to its anti-tubercular actions. Although best known as powerful drugs to treat depression, the monoamine oxidase inhibitors (MAOIs) are also highly effective therapeutic agents for certain anxiety disorders such as panic disorder and social anxiety disorder. MAOIs

Overdose H1 sodium channel H1 death sodium channel are barely prescribed any more today. Only about one in every 3,000 to 5,000 prescriptions for a drug to treat depression is a MAOI and only a few hundred experts prescribe MAOIs out of the hundreds of thousands who prescribe other drugs for depression in the US. Prescribing MAOIs is beginning to become a lost art in psychopharmacology as many familiar with them learned to use MAOIs before the 1990s when SSRIs were introduced and largely replaced MAOIs. Most of these prescribers of MAOIs are now retiring from practice. Nevertheless, MAOIs are a most powerful drug class for unipolar depression and those who prescribe them have seen many patients who respond to nothing else get better on MAOIs. The reader who is an advanced psychopharmacologist should gain familiarity and experience with these agents so that patients who still need them can get them. The reader is referred to specific reviews on MAOIs including some of the author, to help navigate dietary restrictions and drug interactions. The MAOIs phenelzine, tranylcypromine, isocarboxazid, and selegiline are all irreversible enzyme Chapter 7: Treatments for Mood Disorders Figure 7-68 Tricyclic antidepressants and overdose. Tricyclic antidepressants block voltagesensitive sodium channels in the brain (top) and heart (bottom). In overdose, this action can lead to coma, seizures, arrhythmia, and even death. coma seizures arrhythmia inhibitors, and thus enzyme activity returns only after new enzyme is synthesized about 2–3 weeks later. Amphetamine is also a weak but reversible MAOI; some MAOIs have properties related to amphetamine. For example, tranylcypromine has a chemical structure modeled on amphetamine, and thus in addition to MAOI properties, it also has amphetamine-like dopaminereleasing properties. The MAOI selegiline itself

does not have amphetamine-like properties, but is metabolized to both l-amphetamine and l-methamphetamine. Thus, there is a close mechanistic link between some MAOIs and additional amphetamine-like dopamine-releasing actions. MAO Subtypes MAO exists in two subtypes, A and B. The A form preferentially metabolizes the monoamines most closely linked to depression (i.e., serotonin and norepinephrine) whereas the B form preferentially metabolizes trace amines such as phenethylamine (see Chapter 5 and Figures 5-64 through 5-66 for further discussion on trace amines). Both MAO-A and MAO-B metabolize 337

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY dopamine and tyramine, another trace amine. Both MAO-A and MAO-B are in the brain. Noradrenergic neurons (Figure 6-13) and dopaminergic neurons (Figure 4-3) are thought to contain both MAO-A and MAO-B, with MAO-A activity perhaps predominant, whereas serotonergic neurons are thought to contain only MAO-B (Figure 4-37). MAO-A is the major form of this enzyme outside of the brain, with the exception of platelets and lymphocytes, which have MAO-B. Brain MAO-A must be substantially inhibited for antidepressant efficacy to occur (Figure 7-69). This is not surprising, since this is the form of MAO that preferentially metabolizes serotonin and norepinephrine, two of the three monoamines linked to depression and to antidepressant actions, both of which demonstrate increased brain levels after MAO-A inhibition (Figure 7-69). MAO-A, along with MAO-B, also metabolizes dopamine, but inhibition of MAO-A alone does not appear to lead to robust increases in brain dopamine levels since MAO-B can still metabolize dopamine (Figure 7-69). Inhibition of MAO-B is not effective as an antidepressant, as there is no direct effect on either serotonin or norepinephrine metabolism, and little or no dopamine accumulates due to the continued action of MAO-A (Figure 7-70). What therefore is the therapeutic value of MAO-B inhibition? When this enzyme is selectively inhibited, it can boost the action of concomitantly administered levodopa in Parkinson's disease and reduce on/off motor fluctuations. Three MAO-B inhibitors selegiline, rasagiline, and safinamide are approved for use in patients with Parkinson's disease, but are not effective at selective MAO-B doses for the treatment of depression. When MAO-B is inhibited simultaneously with MAO-A, there is robust elevation of dopamine as well as serotonin and norepinephrine (Figure 7-71). This would theoretically provide the most powerful antidepressant efficacy across the range of depressive symptoms, from diminished positive affect to increased negative affect (see Figure 6-41). Thus, MAO-A plus MAO-B inhibition is one of the few therapeutic strategies available to increase dopamine in depression, and therefore to treat refractory symptoms of diminished positive affect. The Dietary Tyramine Interaction One of the biggest barriers to using MAOIs has traditionally been the concern that a patient taking a MAOI may develop a hypertensive crisis after ingesting tyramine in the diet, classically from cheese. Normally, the release of norepinephrine by tyramine is inconsequential because MAO-A safely destroys this released norepinephrine. However, tyramine in the presence of MAO-A inhibition can elevate blood pressure because norepinephrine is not safely destroyed. Every prescriber of MAOIs should counsel patients taking the classic MAOIs about diet and keep up to date with the tyramine content of foods their patients wish to eat. Drug–Drug Interactions for MAOIs While MAOIs are famous for their tyramine reactions, drug–drug interactions are potentially more important clinically. Drug–drug interactions may not only be more common than dietary interactions with tyramine, but some drug interactions can be dangerous or even lethal. Drug interactions with MAOIs are often poorly understood by many practitioners. Since most candidates for MAOI treatment will require treatment with many concomitant drugs over time, including treatment for coughs and colds and for pain, this can prevent psychopharmacologists from prescribing a MAOI if they do not know which drugs are safe to give and which ones must be

avoided. There are two general types of potentially dangerous drug interactions with MAOIs for a practitioner to understand and avoid: those that can raise blood pressure by sympathomimetic actions and those that can cause a potentially fatal serotonin syndrome by serotonin reuptake inhibition. Every prescriber of MAOIs should counsel patients taking the classic MAOIs about drug interactions and keep up to date with the latest warnings about drug interactions of MAOIs with drugs their patients are concomitantly prescribed. Several reviews on these details are available, including some of the author's, and are referenced at the end of the book. DRUGS FOR BIPOLAR DISORDER SPECTRUM Serotonin/Dopamine Blockers: Not Just for Psychosis and Psychotic Mania When D2 blockers were approved for schizophrenia, it was not surprising that these agents would work for psychotic symptoms associated with mania, since the D2 antagonist actions predict efficacy for psychosis in general (discussed in Chapter 5). However, it was somewhat surprising when these dopamine/serotonin blockers proved effective for the core nonpsychotic symptoms of mania (Figure 6-2) and for maintenance treatment to prevent the recurrence of mania. These latter actions are similar to the antimanic therapeutic actions of

Chapter 7: Treatments for Mood Disorders Figure 7-69 Monoamine oxidase A (MAO-A) inhibition. The enzyme MAO-A metabolizes serotonin (5HT) and norepinephrine (NE) as well as dopamine (DA) (left panels). Monoamine oxidase B (MAO-B) also metabolizes DA, but it metabolizes 5HT and NE only at high concentrations (left panels). This means that MAO-A inhibition increases 5HT, NE, and DA (right panels) but that the increase in DA is not as great as that of 5HT and NE because MAO-B can continue to destroy DA (bottom right panel). Inhibition of MAO-A is an efficacious antidepressant strategy. DA boosted moderately 5HT boosted to high concentrations NE boosted to high concentrations MAO-A inhibition MAO-A inhibition MAO-A inhibition A B B A B A A B B A A B A A B A A B MAO-B destroys 5HT only at high concentrations MAO-A destroys 5HT 5HT neuron MAO-B destroys 5HT only at high concentrations 5HT neuron MAO-B destroys 5HT only at high concentrations MAO-B destroys DA MAO-A destroys NE MAO-A destroys DA MAO-A destroys DA NE neuron DA neuron MAO-B destroys DA MAO-A destroys DA MAO-A destroys DA DA neuron MAO-A destroys NE NE neuron MAO-B destroys NE only at high concentrations MAO-B destroys 5HT only at high concentrations MAO-B destroys 5HT only at high concentrations MAO-A Is Inhibited Antidepressant Action

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY DA boosted moderately MAO-B inhibition MAO-B inhibition MAO-B inhibition A B B A B A B B A A B A A B A B A A MAO-B destroys 5HT only at high concentrations MAO-A destroys 5HT MAO-A destroys 5HT 5HT neuron 5HT neuron MAO-B destroys 5HT only at high concentrations MAO-B destroys DA MAO-A destroys NE MAO-A destroys DA MAO-A destroys DA NE neuron DA neuron MAO-B destroys DA MAO-A destroys DA MAO-A destroys DA DA neuron MAO-A destroys NE NE neuron MAO-B destroys NE only at high concentrations MAO-B inhibition irrelevant MAO-B inhibition irrelevant MAO-B Is Inhibited No Antidepressant Action Figure 7-70 Monoamine oxidase B (MAO-B) inhibition. Selective inhibitors of MAO-B do not have antidepressant efficacy. This is because MAO-B metabolizes serotonin (5HT) and norepinephrine (NE) only at high concentrations (top two left panels). Since MAO-B's role in destroying 5HT and NE is small, its inhibition is not likely to be relevant to the concentrations of these neurotransmitters (top two right panels). Selective inhibition of MAO-B also has somewhat limited effects on dopamine (DA) concentrations, because MAO-A continues to destroy DA. However, inhibition of MAO-B does increase DA to some extent, which can be therapeutic in other disease states, such as Parkinson's disease.

Chapter 7: Treatments for Mood Disorders DA boosted to very high concentrations MAO-A+B inhibition MAO-A+B inhibition MAO-A+B inhibition NE boosted to very high concentrations A B B A B A B B A A B A A B A B A A MAO-A and MAO-B Are Inhibited Robust Antidepressant Action Including Dopamine Action 5HT boosted to very high concentrations MAO-B destroys 5HT only at high concentrations MAO-A destroys 5HT 5HT neuron 5HT neuron MAO-B destroys 5HT only at high concentrations MAO-B destroys DA MAO-A destroys NE MAO-A destroys DA MAO-A destroys DA NE neuron DA neuron MAO-A destroys DA DA neuron NE neuron MAO-B destroys NE only at high concentrations Figure 7-71 Combined inhibition of monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B). Combined inhibition of MAO-A and MAO-B may have robust antidepressant actions owing to increases not only in serotonin (5HT) and norepinephrine (NE) but also dopamine (DA). Inhibition of both MAO-A, which metabolizes 5HT, NE, and DA, and MAO-B, which metabolizes primarily DA (left panels), leads to greater increases in each of these neurotransmitters than inhibition of either enzyme alone (right panels).

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY lithium and various anticonvulsant ion channel blockers that act by very different mechanisms (described below). More surprising yet is that some of these same serotonin/ dopamine antagonists/partial agonists are effective for bipolar depression, albeit by mechanisms likely distinct from D2 antagonism/partial agonism. The questions that arise are how serotonin 2/dopamine 2 antagonists and dopamine 2/serotonin 1A partial agonists work in both the manic and depressed poles of bipolar disorder. More recently, some of these same serotonin/dopamine drugs have evidence of efficacy in unipolar depression as augmenting agents to SSRIs/SNRIs when there is inadequate response, as discussed above. Furthermore, some of these same serotonin/dopamine drugs now have additional evidence of efficacy in unipolar and bipolar depression with mixed features of mania. Do they work by the same mechanisms across the entire bipolar spectrum (Figure 6-7)? Is this a class effect of these drugs or do specific drugs work in some but not all parts of the bipolar spectrum? Putative Pharmacological Mechanism of Serotonin/ Dopamine Antagonists/Partial Agonists in Mania The short answer to the question of how serotonin/ dopamine blockers work in mania is that we do not really know. On the one hand, PET scans of patients with mania show the same excessive presynaptic dopamine levels and release in mesostriatal dopamine neurons in acute bipolar mania as for acute psychosis in schizophrenia, described extensively in Chapter 4 and illustrated in Figures 4-15, 4-16, and Figure 5-2. Thus, blocking the excessive dopamine at D2 receptors should have as much of an antimanic effect in bipolar mania as it has an antipsychotic effect in schizophrenia. Indeed, acute bipolar mania is treated with serotonin/dopamine blockers in much the same manner as acute psychosis is treated in schizophrenia, including dosing and expected onset of action within minutes to hours. However, not all agents in the serotonin/dopamine blocker class approved to treat schizophrenia are also approved to treat acute bipolar mania, and not all of those approved for acute bipolar mania are approved for bipolar maintenance (see Table 7-1). Differences in receptor binding profiles could explain why some agents are approved in mania and others not; commercial considerations could also explain why some agents are not approved in mania. To enhance antimanic response and to prevent relapse into another episode of mania, lithium and valproate are commonly used in conjunction with those dopamine/serotonin blockers approved for the treatment of mania, but this is not done for the treatment of schizophrenia, as lithium and valproate do not clearly augment the efficacy of serotonin/dopamine blockers in schizophrenia. Serotonin/Dopamine Antagonists/Partial Agonists across the Depression Spectrum: Bipolar Depression, Depression with Mixed Features, and as Adjuncts to SSRIs/SNRIs in Unipolar Major

Depression The serotonin/dopamine antagonists/partial agonists have proven to be quite versatile therapeutics: from schizophrenia, to mania, to adjuncts for SSRIs/SNRIs in unipolar depression, as we have discussed in this chapter so far. Here we consider the extension of therapeutic use of at least some of the agents in this class to the treatment of bipolar depression and the closely related state of major depressive episodes with mixed features of mania. A major paradigm shift is afoot in the treatment of bipolar depression and depression with mixed features. We used to ask: “Don’t we treat all forms of depression with so-called antidepressants, drugs that inhibit the reuptake of monoamines?” Although most patients with depression, including those with bipolar depression and depression with mixed features, do receive monoamine reuptake inhibiting drugs, the modern answer to this question is increasingly becoming a resounding “No!!” Practice guidelines and US FDA approvals are moving away from the treatment of bipolar depression or depression with mixed features with the standard monoamine reuptake inhibiting agents that are so commonly used for the treatment of unipolar depression. Reuptake inhibitors are increasingly reserved to treat patients with unipolar depression only if they do not have mixed features, and patients with bipolar depression only as second-line agents to augment other agents. Best practice is evolving for bipolar depression or depression with mixed features, so now first-line treatment is one of the specifically approved serotonin/dopamine blockers, not a monoamine reuptake inhibitor. However, there is plenty of controversy over this recommendation, as many prescribers and some experts still advocate for monoamine reuptake inhibitors in some patients with bipolar depression. But more and more studies are showing failure of the monoamine reuptake inhibiting drugs to work consistently in bipolar depression or in mixed features, and, furthermore, monoamine reuptake inhibitors can induce intolerable activating side effects and even manic episodes and suicidality in patients with bipolar/mixed depression. Other studies do show

some benefits of monoamine reuptake blockers in bipolar depression, and in fact fluoxetine combined with olanzapine is approved for bipolar depression (Table 7-1). However, no agent at all is approved for depression with mixed features. The studies that do exist suggest poor responses of mixed features to the well-known monoamine reuptake inhibitors and an expanding evidence base for the use of certain serotonin/dopamine blockers, particularly those already approved for bipolar depression, as the preferred treatment for mixed features as well (see Table 7-1). We do not know whether any and all drugs with serotonin/dopamine blocking properties that are normally used to treat psychosis would be effective for bipolar depression, as some have not been studied and others have failed in clinical trials; nor are we certain of the antidepressant mechanism of action of those that are approved. However, each of the serotonin/dopamine agents now approved to treat bipolar depression was originally developed to treat psychosis, and their proposed mechanism of antidepressant therapeutic action in bipolar depression and depression with mixed features is presented in the following sections. Olanzapine–Fluoxetine As previously mentioned, olanzapine–fluoxetine combination (Figures 5-44 and 7-16) is approved for schizophrenia, bipolar mania, treatment-resistant unipolar depression, and bipolar depression. Post hoc analyses of mania with mixed features of depression also suggest efficacy of olanzapine for mania with mixed features of depression, although the counterpart to this condition at the other end of the spectrum, depression with mixed features of mania (Figures 6-3 through 6-7), has not been studied (Table 7-1). 5HT2A antagonist actions combined with 5HT2C antagonism are likely candidates to be linked to antidepressant action in bipolar depression (“treatment from below”; see Figure 7-8). D2 antagonism could theoretically help keep the lid on treatment from below so it doesn’t spill over into activation and mania. Quetiapine As previously mentioned, quetiapine (Figure 5-45) is

approved for schizophrenia, bipolar mania, and for augmentation of SSRIs/SNRIs in treatment-resistant unipolar depression. It is also approved in bipolar depression. Like olanzapine, post hoc analyses of Chapter 7: Treatments for Mood Disorders quetiapine treatment of mania with mixed features of depression also suggest efficacy, although depression with mixed features of mania has not been studied (Table 7-1). 5HT2A antagonist actions combined with 5HT2C and α2 antagonism, as well as agonist actions at 5HT1A receptors, are likely candidates to be linked to antidepressant action in bipolar depression (treatment from below). Like olanzapine, D2 antagonism by quetiapine could theoretically help keep the lid on treatment from below so it doesn't spill over into activation and mania. Lurasidone Although approved for the treatment of schizophrenia, lurasidone (Figure 5-53) was never tested nor approved for the treatment of mania (Table 7-1). Lurasidone has several hypothetical antidepressant receptor binding properties: blockade of 5HT2A (Figure 5-17C), 5HT7 (7-53C), and α2 receptors (Figure 7-41), with agonist actions at 5HT1A receptors (Figure 5-22). It is one of the only agents to show on post hoc analysis of bipolar depression that those with bipolar depression and mixed features respond as well to lurasidone as patients with bipolar depression without mixed features. Perhaps more importantly, lurasidone is the only agent to be studied in a large, randomized multicenter trial of unipolar depression with mixed features and to demonstrate robust antidepressant efficacy in this group without induction of mania. Lurasidone is prescribed for bipolar depression and for mixed features at doses lower than those generally used for the treatment of psychosis in schizophrenia, and is generally well tolerated with little propensity for weight gain or metabolic disturbances and is one of the most widely prescribed agents for bipolar depression. Cariprazine Cariprazine (Figure 5-58) is a D3/D2/5HT1A partial agonist approved for the treatment of acute bipolar mania and for bipolar depression, with ongoing trials as an adjunct to SSRI/SNRIs in unipolar depression (Table 7-1). Cariprazine has 5HT1A partial agonist actions as well as α1 (Figure 7-58) and α2 (Figure 7-41) antagonist actions, each with potential antidepressant mechanisms. What sets cariprazine apart from other agents in this group of serotonin/dopamine antagonists/partial agonists is its unique highly potent action at D3 dopamine receptors as a partial agonist. Cariprazine is the most potent of any available agent and much more potent than dopamine itself for the D3 receptor. How is D3 antagonism/partial 343

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-72 Dopamine 3 binding affinity: dopamine versus serotonin/dopamine antagonists/partial agonists. Dopamine 3 antagonism/partial agonism may confer therapeutic benefit in bipolar depression with or without mixed features. Although many agents may bind to the D3 receptor, only two – cariprazine and blonanserin – have multiple orders of magnitude higher affinity for the D3 receptor than does dopamine (DA) itself, thus allowing them to compete successfully with dopamine for receptor occupancy. Three orders of magnitude higher affinity than DA Cariprazine binding affinity for D3 (0.09nM) Blonanserin binding affinity for D3 (0.28nM) Brexpiprazole binding affinity for D3 (1.1nM) Iloperidone binding affinity for D3 (10.5nM) Clozapine binding affinity for D3 (304.6nM) Quetiapine binding affinity for D3 (800nM) Lurasidone binding affinity for D3 (15.7nM) Aripiprazole binding affinity for D3 (17.7nM) Olanzapine binding affinity for D3 (39.5nM) Asenapine binding affinity for D3 (1.8nM) Paliperidone binding affinity for D3 (2.6nM) Ziprasidone binding affinity for D3 (7.3nM) Risperidone binding affinity for D3 (8.0nM) Two orders of magnitude higher affinity than DA One order of magnitude higher affinity than DA One order of magnitude lower affinity than DA Two orders of magnitude lower affinity than DA Three orders of magnitude lower affinity than DA DA binding affinity for D3 (Ki=60nm) agonism linked to therapeutic efficacy in bipolar depression with or without mixed features? We extensively discussed drugs that are antagonists or partial agonists at D2 receptors in Chapter 5 and how they

are used for psychotic illnesses. The same agents also act at D3 receptors, but at clinical doses only two of them – cariprazine and blonanserin (Chapter 5, Figure 5-62) – can highly successfully compete with dopamine itself for the D3 receptor (Figure 7-72). That is, in the brain, drugs compete with dopamine itself for the D3 receptor and only those drugs with an affinity for the D3 receptor significantly higher than dopamine's affinity for the D3 receptor will actually block the D3 receptor. Several agents have somewhat higher affinity for the D3 receptor than dopamine, and may have some net effect blocking the D3 receptor, but cariprazine clearly has the most potent action at the D3 receptor and would be expected to block D3 receptors substantially at clinical dosing (Figure 7-72). What happens when you block a D3 receptor? Recall that dopamine has five receptor subtypes (see discussion in Chapter 4 and Figure 4-5) in two different groups (Figure 4-4). D3 receptors can be presynaptic and postsynaptic (Figures 4-4 through 4-9). Postsynaptic blockade of D3 receptors in limbic regions may contribute to antipsychotic actions but it is the presynaptic actions of D3 antagonism/partial agonism in the ventral tegmental area (VTA) that are of most interest for explaining cariprazine's antidepressant actions (Figure 7-73). So, what is the consequence of blocking D3 receptors in the VTA and why might this contribute to antidepressant actions of cariprazine? Recall also that dopamine input to the cortex is thought to be deficient in mood, motivation, and cognitive symptoms of depression and also in the negative symptoms of schizophrenia, due in part to hypothetically deficient dopamine release from mesocortical dopamine neurons. These neurons are depicted in Figure 7-73A and show D3 presynaptic

Chapter 7: Treatments for Mood Disorders Figure 7-73 Dopamine 3 antagonism/partial agonism in the ventral tegmental area (VTA). (A) Presynaptic D3 receptors detect dopamine and inhibit further dopamine release. These receptors are present in the VTA but not in the prefrontal cortex. There are, however, postsynaptic D2 receptors in the prefrontal cortex, which are stimulated by dopamine. Shown here is the mesocortical dopamine pathway, with stimulation of D3 receptors resulting in reduced dopamine release in the prefrontal cortex. Low levels of dopamine in the prefrontal cortex is hypothesized to contribute to depressed mood, reduced motivation, and cognitive symptoms, all of which occur in mood disorders, as well as to negative symptoms in schizophrenia. (B) Antagonism/partial agonism of D3 receptors in the VTA can increase dopamine release in the prefrontal cortex. Because there are no D3 receptors in the prefrontal cortex, D3 antagonists/ partial agonists have no effect there. Dopamine is free to stimulate D1 receptors, hypothetically improving symptoms of depression. negative symptoms A B affective symptoms Mesocortical Dopamine Pathway D3 D3 antagonist/ partial agonist D1 D1 (SIGH) negative symptoms affective symptoms (SIGH) autoreceptors in the VTA on dopamine cell bodies for a population of mesocortical neurons. The function of these D3 receptors is to detect dopamine and inhibit further dopamine release (Figure 7-73A). However, these same neurons projecting to the prefrontal cortex do not have presynaptic autoreceptors on their axon terminals (see Chapter 4 discussion and Figure 4-9; see also Figure 7-73). D3 antagonists will have no effect in the prefrontal cortex since there are few D3 receptors there. In Chapter 4 we discussed how most of the dopamine receptors in prefrontal cortex are postsynaptic and D1 (Figure 4-9). What this means is that when D3 antagonists/partial agonists act in the VTA to block them, this disinhibits the dopamine neurons projecting to prefrontal cortex and they release dopamine onto D1 receptors (Figure 7-73B). This action hypothetically improves symptoms of depression and is one explanation for why cariprazine has antidepressant actions, and also why it has more robust improvement of negative symptoms of schizophrenia than other drugs for psychosis. Improvement in energy, motivation, and "brightening" are observed after D3 antagonism in patients with both mood

disorders and schizophrenia, and animal models demonstrate precognitive actions and also improvements in substance abuse. Cariprazine is approved for acute bipolar mania and for acute bipolar depression (Table 7-1). Post hoc analyses show significant clinical improvement both in mania with mixed features of depression and bipolar depression with mixed features of mania. Studies as adjunctive treatment for patients with unipolar depression on SSRIs/SNRIs have early indications of efficacy reported. Thus, cariprazine has some of the most robust and wide-ranging efficacy known across the entire bipolar spectrum (Figure 6-7). Lithium, the Classic “Antimanic” and “Mood Stabilizer” Bipolar mania has classically been treated with lithium for more than 50 years. Lithium is an ion whose mechanism of action is not certain. Candidates for its mechanism of action are various signal transduction sites beyond neurotransmitter receptors (Figure 7-74). This includes second messengers such as the phosphatidyl inositol system, where lithium inhibits the enzyme inositol monophosphatase; modulation of G proteins; and, most recently, regulation of gene expression for growth factors and neuronal plasticity by interaction with downstream signal transduction cascades, including

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Possible Mechanism of Lithium Action on Downstream Signal Transduction Cascades neurotrophin NT1 NT G E P GSK-3 promotes neuroprotection long-term plasticity antimanic / mood stabilizer = lithium inhibition of GSK-3 (glycogen synthase kinase 3) and protein kinase C (Figure 7-74). However lithium works, it is proven effective in manic episodes, and in maintenance of recurrence, especially for manic episodes and, perhaps to a lesser extent, for depressive episodes. Lithium is well established to help prevent suicide in patients with mood disorders. It is also used to treat depressive episodes in bipolar disorder and as an augmenting agent to drugs for depression in treatment-resistant unipolar depression, but is not formally approved for these uses. A number of factors have led to an unfortunate decline in the use of lithium in recent years, including the entry of multiple new treatment options into the therapeutic armamentarium for bipolar disorder, the side effects of lithium, and the monitoring burden that is part of prescribing lithium. The modern use of lithium by experts departs from its classic use as a high-dose monotherapy for euphoric mania, with lithium often utilized now as one member of a portfolio of treatments, often allowing once-daily administration and at lower doses when combined with other mood stabilizers. Well-known side effects of lithium include gastrointestinal symptoms such as dyspepsia, nausea, vomiting, and diarrhea, as well as weight gain, hair loss, acne, tremor, sedation, decreased cognition, and incoordination. There are also potential long-term Figure 7-74 Lithium’s mechanism of action. Although lithium is the oldest treatment for bipolar disorder, its mechanism of action is still not well understood. Several possible mechanisms exist and are shown here. Lithium may work by affecting signal transduction, perhaps through its inhibition of second-messenger enzymes such as inositol monophosphatase (right), by modulation of G proteins (middle), or by interaction at various sites within downstream signal transduction cascades, including glycogen synthase kinase 3 (GSK-3) (left). ++ ++ adverse effects upon the thyroid and kidney. Lithium has a narrow therapeutic window, requiring monitoring of plasma drug levels. Anticonvulsants as “Mood Stabilizers” Based upon theories that mania may “kindle” further episodes of mania, a logical parallel with seizure disorders was drawn, since seizures can “kindle” more seizures. Several anticonvulsants (Table 7-3) are categorized on the basis of whether they are “mania-minded,” i.e., treat from above and stabilize from above (Figure 7-7); “depressionminded,” i.e., treat from below and stabilize from below (Figure 7-8); or both. Because the known anticonvulsants carbamazepine and valproate proved effective in treating the manic phase of bipolar disorder, this has led to the idea that any

anticonvulsant would be a mood stabilizer, especially for mania. However, this has not proven to be the case (Table 7-3) since anticonvulsants do not all act by the same pharmacological mechanisms, as discussed below. These agents for mania or bipolar depression are better classified for their pharmacological mechanism of action at ion channels rather than as “mood stabilizers” or “anticonvulsants.” Numerous mood stabilizers that are also anticonvulsants are discussed below, including not only those with proven efficacy in different phases of bipolar disorder, but also those with dubious efficacy in bipolar disorder (Table 7-3).

Chapter 7: Treatments for Mood Disorders Anticonvulsants with Proven Efficacy in Bipolar Disorder Valproic Acid (Valproate, Sodium Valproate) As for all anticonvulsants, the exact mechanism of action of valproic acid (also, sodium valproate, valproate) is uncertain; however, even less may be known about the mechanism of valproate than for other anticonvulsants. Various hypotheses are discussed here, and summarized in Figures 7-75 through 7-78. At least three possibilities exist for how valproic acid works: inhibiting voltage-sensitive sodium channels (Figure 7-76), boosting the actions of the neurotransmitter GABA (γ-aminobutyric acid) (Figure 7-77), and regulating downstream signal transduction cascades (Figure 7-78). It is not known whether these actions explain the mood-stabilizing actions, the anticonvulsant actions, the anti-migraine actions, or the side effects of valproic acid. Obviously, this simple molecule has multiple and complex clinical effects, and research is trying to determine which of the various possibilities explain the “mood-stabilizing” antimanic effects of valproic acid so that new agents with more efficacy and fewer side effects can be developed by targeting the relevant pharmacological mechanism for bipolar disorder. One hypothesis to explain mood-stabilizing antimanic actions is the possibility that valproate acts to diminish excessive neurotransmission by diminishing the flow of ions through voltage-sensitive sodium channels (VSSCs) (Figure 7-76). VSSCs are discussed in Chapter 3 and illustrated in Figures 3-19 through 3-21. No specific molecular site of action for valproate has been identified, but it is possible that valproate may change the sensitivity of sodium channels by altering phosphorylation of Table 7-3 Anticonvulsant mood stabilizers Agent Putative clinical actions Epilepsy Mania-minded Depression-minded Treat from above Stabilize from above Treat from below Stabilize from below Valproate ++++ ++++ ++ + +/− Carbamazepine ++++ ++++ ++ + +/− Lamotrigine ++++ +/− ++++ +++ ++++ Oxcarbazepine/licarbazepine ++++ ++ + +/− +/− Riluzole + + +/− Topiramate ++++ +/− +/− Gabapentin ++++ +/− +/− Pregabalin ++++ +/− +/− Figure 7-75 Valproic acid. Shown here is an icon of the pharmacological actions of valproic acid, an anticonvulsant used in the treatment of bipolar disorder. Valproic acid (also valproate) may work by interfering with voltage-sensitive sodium channels, enhancing the inhibitory actions of γ-aminobutyric acid (GABA), and regulating downstream signal transduction cascades, although which of these actions may be related to mood stabilization is not clear. Valproate may also interact with other ion channels, such as voltage-sensitive calcium channels, and also indirectly block glutamate (Glu) actions. valproic acid Ca Glu Na GABA ++ +

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 7-76 Possible sites of action of valproate on voltage-sensitive sodium channels (VSSCs). Valproate may exert antimanic effects by changing the sensitivity of VSSCs, perhaps by directly binding to channel subunits or inhibiting phosphorylating enzymes that regulate the sensitivity of these ion channels. Inhibition of VSSCs would lead to reduced sodium influx and, in turn, potentially to reduced glutamate excitatory neurotransmission, which is a possible mechanism for mania efficacy. Possible Sites of Action of Valproate on VSSCs = valproate G E P P04 G E P Possible Sites of Action of Valproate on GABA inactive substance GABA-T

GABA neuron GABA ? ? ? E = valproate Figure 7-77 Possible sites of action of valproate on γ-aminobutyric acid (GABA). Valproate's antimanic effects may be due to enhancement of GABA neurotransmission, perhaps by inhibiting GABA reuptake, enhancing GABA release, or interfering with the metabolism of GABA by GABA-T (GABA transaminase).

sodium channels, either by binding directly to the VSSC or its regulatory units, or by inhibiting phosphorylating enzymes (Figure 7-76). If less sodium is able to pass into neurons, this may lead to diminished release of glutamate and therefore less excitatory neurotransmission, but this is only a theory. There may be additional effects of valproate on other voltage-sensitive ion channels, but these are poorly characterized and may relate to side effects as well as to therapeutic effects. Another idea is that valproate enhances the actions of GABA, either by increasing its release, decreasing its reuptake, or slowing its metabolic inactivation (Figure 7-77). The direct site of action of valproate that causes the enhancement of GABA remains unknown, but there is good evidence that the downstream effect of valproate ultimately does result in more GABA activity, and thus more inhibitory neurotransmission, possibly explaining antimanic actions. Finally, a number of downstream actions on complex signal transduction cascades have been described (Figure 7-78). Like lithium, valproate may inhibit GSK-3, but it may also target many other downstream sites, from blockade of phosphokinase C (PKC) and MARCKS (myristoylated alanine-rich C kinase substrate), to activating various signals that promote neuroprotection and long-term Possible Sites of Action of Valproate on Downstream Signal Transduction Cascades neurotrophin Ras/Raf/MEK ERK activation P GSK-3 promotes neuroprotection long-term plasticity antimanic / mood stabilizer = valproate BCL2 activation GAP43 activation neuronal genome Chapter 7: Treatments for Mood Disorders plasticity such as ERK (extracellular signal-regulated kinase) kinase, BCL2 (cytoprotective protein B-cell lymphoma/leukemia-2 gene), GAP43 (growth associated protein 43), and others (Figure 7-78). The effects of these signal transduction cascades are only now being clarified, and which of these possible effects of valproate might be relevant to mood-stabilizing actions are not yet understood. Valproate is proven effective for the acute manic phase of bipolar disorder, and is commonly used long-term to prevent recurrence of mania, although its prophylactic effects have not been as well established as its acute effects in mania (Table 7-3). Antidepressant actions of valproate have also not been well established, nor has it been shown to convincingly stabilize against recurrent depressive episodes, but there may be some efficacy for the depressed phase of bipolar disorder in some patients. Some experts believe valproic acid is more effective than lithium for rapid cycling and mixed episodes of mania. In reality, such episodes are very difficult to treat, and combinations of two or more mood stabilizers, including lithium plus valproate plus serotonin/dopamine blockers, are usually in order. For optimum efficacy, it may be ideal to push the dose of valproate, but no drug works if your patient refuses to take it, and valproic acid often Figure 7-78 Possible sites of action of valproate on downstream signal transduction cascades. Valproate has been shown to have multiple downstream effects on signal transduction cascades, which may be involved in its antimanic effects. Valproate inhibits glycogen synthase kinase 3 (GSK-3), phosphokinase C (PKC), and myristoylated alaninerich C kinase substrate (MARCKS). In addition, valproate activates signals that promote neuroprotection and long-term plasticity, such as extracellular signal-regulated kinase (ERK), cytoprotective protein B-cell lymphoma/leukemia-2 gene (BCL2), and growth associated protein 43 (GAP43). NT1 GE PKC MARCKS 349

 has unacceptable side effects such as hair loss, weight gain, and sedation. Certain problems can be avoided by lowering the dose, but this will

generally lower efficacy, and thus there may be the requirement to combine valproate with other mood stabilizers, especially when valproate is given in lower doses. Some side effects may be related more to chronicity of exposure rather than to dose and thus may not be avoidable by reducing the dose. This includes warnings for bone marrow, liver, pancreatic, and fetal toxicities such as neural-tube defects, as well as concerns about weight gain, metabolic complications, and possible risk of amenorrhea and polycystic ovaries in women of child-bearing potential. A syndrome of menstrual disturbances, polycystic ovaries, hyperandrogenism, obesity, and insulin resistance may be associated with valproic acid therapy in such women. Carbamazepine Carbamazepine (Figure 7-79) was actually the first to be shown to be effective in the manic phase of bipolar disorder, but did not receive US FDA approval until recently as a once-daily controlled-release formulation. Although carbamazepine and valproate both act effectively on the manic phase of bipolar disorder (Table carbamazepine ++ Ca + K GABA + Na channel unit Figure 7-79 Carbamazepine. Shown here is an icon of the pharmacological actions of carbamazepine, an anticonvulsant used in the treatment of bipolar disorder. Carbamazepine may work by binding to the α subunit of voltage-sensitive sodium channels (VSSCs) and could perhaps have actions at other ion channels for calcium and potassium. By interfering with voltagesensitive channels, carbamazepine may enhance the inhibitory actions of γ-aminobutyric acid (GABA). 7-3), they appear to have different pharmacological mechanisms of action, including different side-effect profiles. Thus, carbamazepine is hypothesized to act by blocking voltage-sensitive sodium channels (VSSCs) (Figure 7-80), perhaps at a site within the channel itself, also known as the α subunit of VSSCs. As mentioned earlier, VSSCs are discussed in Chapter 3 and illustrated in Figures 3-19 through 3-21. The hypothesized action of carbamazepine upon the α subunit of VSSCs (Figure 7-80) is different from the hypothesized actions of valproate on these sodium channels (Figure 7-76), but may be similar to how the anticonvulsants oxcarbazepine and its active metabolite eslicarbazepine also act. Although both carbamazepine and valproate are anticonvulsants and both treat mania from above, there are differences between these two “anticonvulsants” beyond their presumed pharmacological mechanisms of therapeutic action in mania. For example, valproate is proven effective in migraine, but carbamazepine is proven effective in neuropathic pain. Furthermore, carbamazepine has a different side-effect profile than valproate, including more profound immediate suppressant effects upon the bone marrow, requiring initial monitoring of blood counts (blood counts including platelets should also be periodically monitored on valproate), and notable induction of the cytochrome P450 enzyme 3A4. Both carbamazepine and valproate are sedating and can cause fetal toxicity such as neural-tube defects. Lamotrigine Lamotrigine (Figure 7-81) is approved as a “mood stabilizer” for entirely different clinical indications than the anticonvulsant mood stabilizers valproate and carbamazepine, making the point that anticonvulsants do not all have the same therapeutic actions in bipolar disorder. Lamotrigine is not approved to treat mania or depression in bipolar disorder, but is approved to prevent recurrence of both mania and depression in bipolar disorder. There are many curious things about lamotrigine as a “mood stabilizer.” First, the US FDA has not approved its use for acute bipolar depression, yet most experts believe that lamotrigine is effective for bipolar depression. A second interesting thing about lamotrigine is that even though it has some overlapping mechanistic actions with carbamazepine, namely binding to the open-channel conformation of VSSCs (Figure 7-82), lamotrigine is not approved for bipolar mania. Perhaps lamotrigine’s pharmacological actions are not potent enough at sodium channels, or perhaps the long

carbamazepine lamotrigine ++ Ca + K + Na channel Glu unit Figure 7-81 Lamotrigine. Shown here is an icon of the pharmacological actions of lamotrigine, an anticonvulsant used in the treatment of bipolar disorder. Lamotrigine may work by blocking the alpha subunit of voltage-sensitive sodium channels (VSSCs) and could perhaps also have actions at other ion channels for calcium and potassium. Lamotrigine is also thought to reduce the release of the excitatory neurotransmitter glutamate. Chapter 7: Treatments for Mood Disorders Figure 7-80 Binding site of carbamazepine. Carbamazepine is believed to bind to a site located within the open-channel conformation of the voltagesensitive sodium channel (VSSC) α subunit. Possible Sites of Action of Lamotrigine on Glutamate Release glutamate neuron lamotrigine lamotrigine Figure 7-82 Possible site of action of lamotrigine on glutamate release. It is possible that lamotrigine reduces glutamate release through its blockade of voltage-sensitive sodium channels (VSSCs). Alternatively, lamotrigine may have this effect via an additional synaptic action that has not yet been identified. 351

 titration period required when starting lamotrigine makes it difficult to show any useful effectiveness for mania, which generally requires treatment with drugs that can work quickly. A third aspect of lamotrigine is that it is generally well tolerated, with one glaring exception: a propensity to cause rashes, including (rarely) the life-threatening Stevens Johnson syndrome (toxic epidermal necrolysis). Rashes caused by lamotrigine can be minimized by very slow up-titration of the drug during initiation of therapy, avoiding or managing drug interactions, such as those with valproate that raise lamotrigine levels, and by understanding how to identify and manage serious rashes, including being able to distinguish them from benign rashes (see discussion of lamotrigine in Stahl's Essential Psychopharmacology: the Prescriber's Guide). Finally, lamotrigine seems to have some unique aspects to its mechanism of action (Figure 7-82), namely to reduce the release of the excitatory neurotransmitter glutamate. It is not clear whether this action is secondary to blocking the activation of VSSCs (Figure 7-82) or to some additional synaptic action. Reducing excitatory glutamatergic neurotransmission, especially if excessive during bipolar depression, may be a unique mechanism of action of lamotrigine and explain why it has such a different clinical profile as a treatment from below and a stabilizer from below for bipolar depression. Anticonvulsants with Uncertain or Doubtful Efficacy in Bipolar Disorder Oxcarbazepine/Eslicarbazepine Oxcarbazepine is structurally related to carbamazepine, but is not a metabolite of carbamazepine. Oxcarbazepine is actually not the active form of the drug, but a prodrug that is immediately converted into a 10-hydroxy derivative, also called the monohydroxy derivative, and most recently has been named licarbazepine. The active form of licarbazepine is the S enantiomer, known as eslicarbazepine. Thus, oxcarbazepine really works via conversion to eslicarbazepine, which is itself now available as an anticonvulsant. Oxcarbazepine has a presumed mechanism of anticonvulsant action the same as that for carbamazepine, namely, binding to the open-channel conformation of the VSSC at a site within the channel itself on the α subunit (as in Figure 7-80). However, oxcarbazepine seems to have some important differences from carbamazepine, including being less sedating, having less bone marrow toxicity, and also having less CYP450 3A4 interactions, making it a more tolerable agent that is easier to dose. On the other hand, oxcarbazepine has never been proven to work in acute bipolar mania or depression. Nevertheless, because of a similar postulated mechanism of action but a better tolerability profile, oxcarbazepine and more recently eslicarbazepine have been utilized "off-label" by many clinicians especially for the manic phase of bipolar disorder. Topiramate Topiramate is another compound approved as an anticonvulsant and for migraine, and recently, in combination with bupropion, for weight loss in obesity. Topiramate has been tested in bipolar disorder, but with

ambiguous results (Table 7-3). It does seem to be associated with weight loss and is sometimes given as an adjunct to drugs for psychosis or to mood stabilizers that cause weight gain, but can cause unacceptable sedation in some patients. Topiramate is also being tested in various substance abuse disorders, including stimulant abuse and alcoholism. However, topiramate is not clearly effective as a mood stabilizer, either from evidence-based randomized controlled trials (which are not consistently positive) or from clinical practice. Gabapentin and Pregabalin These anticonvulsants seem to have little or no action as mood stabilizers, yet are robust treatments for various pain conditions, from neuropathic pain to fibromyalgia, and for various anxiety disorders, and are discussed in more detail in Chapter 8 on anxiety and Chapter 9 on pain. Calcium Channel Blockers (L-Type) There are several types of calcium channels, not only the N or P/Q channels linked to secretion of neurotransmitters, targeted by α2δ ligands and discussed in Chapter 3 (see Figures 3-23 and 3-24), but also L channels localized on vascular smooth muscle and which are targeted by various antihypertensive and antiarrhythmic drugs, commonly called “calcium channel blockers.” L-type channels are located on neurons where their function is still being debated, and some anecdotal evidence suggests that calcium channel blockers, especially dihydropyridine-type calcium channel blockers, may be useful for some patients with bipolar disorder. Riluzole This agent has anticonvulsant actions in preclinical models, but was developed to slow the progression

of amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease). Theoretically, riluzole binds to VSSCs and prevents glutamate release, in an action similar to that postulated for lamotrigine (see Figure 7-82). The idea is that diminishing glutamate release in ALS would prevent the postulated excitotoxicity that may be causing death of motor neurons in ALS. Excessive glutamate activity may be occurring not only in ALS, but also in bipolar depression, although this is not necessarily so severe as to cause widespread neuronal loss. Combinations are the Standard for Treating Bipolar Disorder Given the disappointing number of patients who attain satisfactory response in bipolar disorder from monotherapy, it is more the rule than the exception that bipolar patients receive combination treatments. Although first-line treatment may be one of the serotonin/dopamine agents, if this fails to adequately control mania, another treatment for mania such as valproate or lithium may be added (Figure 7-83). On the other hand, if serotonin/dopamine agents fail to adequately control depression, lamotrigine may be added or, controversially, a monoamine reuptake inhibitor (Figure 7-83). The goal is four treatments for fullest Combos for Bipolar Disorder Evidence-Based Bipolar Combos for Mania + 5HT/DA blocker-lithium combo lithium 5HT/DA blocker + valproate 5HT/DA blockervalproate combo 5HT/DA blocker Practice-Based Bipolar Combos for Depression + 5HT/DA blockerLamictal combo 5HT/DA blocker Lamictal/ lamotrigine Careful Combo + + 5HT/DA blockerLamictal combo 5HT/DA blocker Lamictal/ lamotrigine monoamine reuptake blocker Chapter 7: Treatments for Mood Disorders remission of symptoms: treat from above and stabilize from above (Figure 7-7) and treat from below and stabilize from below (Figure 7-8). FUTURE TREATMENTS FOR MOOD DISORDERS Dextromethorphan–Bupropion and Dextromethorphan–Quinidine As discussed above, one of the most interesting developments in the treatment of resistant unipolar depression in recent years has been the observation that infusions of subanesthetic doses of ketamine or intranasal administration of esketamine can exert an immediate antidepressant effect and can often immediately reduce suicidal thoughts. Since the effects are often not sustained for more than a few days, investigators have searched for oral ketamine-like agents that could have rapid onset, sustained efficacy, greater ease of administration, and better tolerability in patients with treatment-resistant illness. Several such possibilities are in development, namely various NMDA antagonists with additional pharmacological

properties. One agent combines the NMDA antagonist dextromethorphan with the CYP450 2D6 inhibitor and NDRI bupropion (also known as AXS-05), and the other Figure 7-83 Bipolar disorder combinations. Most patients with bipolar disorder will require treatment with two or more agents. The combinations with the most evidence for mania include addition of a serotonin/dopamine antagonist to either lithium or valproate. Combinations that are not well studied in controlled trials but that have some practice-based evidence for depression include a serotonin/ dopamine antagonist plus lamotrigine. Although controversial, some clinicians add a monoamine reuptake inhibitor to a serotonin/dopamine antagonist for bipolar depression. 353

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY combines dextromethorphan with the CYP450 2D6 inhibitor quinidine (Figure 7-84). The latter combination has already been approved to treat pathological laughing and crying in pseudobulbar affect. A newer version of the latter combination has deuterated the dextromethorphan molecule and altered the dose of quinidine (Figure 7-85). Deuteration extends the half-life of a compound and allows re-patenting for commercial development (deuteration of tetrabenazine was previously discussed in Chapter 5 in the section on treatment of tardive dyskinesia and illustrated in Figure 5-11B). Although it is clear that dextromethorphan has clinically relevant affinity for the NMDA receptor, other binding properties are less well characterized, including σ1 receptor binding, SERT inhibition, and weak μ-opioid binding (Figure 7-84). As for all NMDA receptor antagonists studied for treatment-resistant depression, it is unclear which subtypes of NMDA receptor are engaged by dextromethorphan, which are most important, and what the role of σ1 or μ-opioid binding is in rapid antidepressant action. Dextromethorphan is rapidly metabolized by CYP450 2D6 making it difficult to achieve therapeutic blood levels following oral administration without dextromethorphan (DXM) NMDA α1D σ1 SERT SERT α1D ++ NMDA + + σ1 + + + bupropion quinidine DAT 2D6 2D6 NET NDRI concomitant administration of a CYP450 2D6 inhibitor. Each combination product adds a 2D6 inhibitor (Figure 7-84). Quinidine is a 2D6 inhibitor at doses below its cardiovascular actions, and bupropion is not only an NDRI (Figures 7-34 and 7-35) but also a 2D6 inhibitor. For bupropion, as discussed above and illustrated in Figures 7-34 and 7-35, in addition to 2D6 inhibition there is the monoamine-associated antidepressant mechanism of NRDIs (Figure 7-84) with the potential for synergy with the NMDA antagonist mechanism of dextromethorphan. Both combination products are in trials for treatmentresistant depression with some promising initial results, especially for dextromethorphan–bupropion, which has been awarded breakthrough therapy status by the US FDA for major depressive disorder and fast-track designation for treatment-resistant depression. Both combination products are also in trials for agitation in Alzheimer disease and show some promising initial results, especially for dextromethorphan–bupropion, wh ich was given fast-track designation by the FDA. Dextromethorphan–bupropion treatment of agitation in dementia is discussed further in Chapter 12 on dementia. Figure 7-84 Dextromethorphan– bupropion and dextromethorphan– quinidine. Dextromethorphan is a weak N-methyl-D-aspartate (NMDA) receptor antagonist, with stronger binding affinity for the serotonin transporter (SERT) and σ1 receptors. It is rapidly metabolized by CYP450 2D6, making it difficult to achieve therapeutic blood levels without concomitant administration of a CYP450 2D6 inhibitor. Dextromethorphan is being studied in combination with the norepinephrine–dopamine reuptake inhibitor (NDRI) bupropion, which also inhibits CYP450 2D6, and in combination with the CYP450 2D6 inhibitor quinidine. quinidine

deuterated dextromethorphan (Deu-DXM) NMDA α1D σ1 Deu-DXM SERT σ α1D ++ NMDA + + + Dextromethadone Methadone is a racemic mixture of dextro- and levomethadone and is given

orally as a μ-opioid agonist for medication-assisted treatment of opioid use disorder. The μ-opioid activity resides mostly in the levo enantiomer, and the dextro enantiomer has relatively more potent NMDA antagonist activity, without as potent μ-opioid agonist activity. The dextro enantiomer (Figure 7-86) is in clinical development as a rapid-onset treatment of major depression with some promising early clinical results. Just as for all NMDA antagonists for treatment-resistant depression (i.e., ketamine, esketamine, and dextromethorphan), the relative importance of NMDA antagonism, the specific NMDA receptors targeted, and the downstream consequences of NMDA antagonism are just now being clarified, including the potential differences amongst these various NMDA antagonists. Furthermore, the additional binding properties of each of these agents, including Chapter 7: Treatments for Mood Disorders Figure 7-85 Deuterated dextromethorphan. A deuterated formulation of dextromethorphan in combination with quinidine is in development. Deuteration extends the half-life of dextromethorphan, which in turn affects the required dose of quinidine. SERT dextromethadone, are less well characterized, such as σ1 receptor binding, SERT inhibition, and weak μ-opioid binding (Figure 7-86). It is possible that these agents do not act simply as NMDA antagonists, but that some degree of μ-opioid agonist activity may shepherd dimers of NMDA and μ receptors by exploiting their natural oppositional actions, to create a greater NMDA effect in the presence of μ stimulation than in the absence of it. This is the subject of much further research as the field attempts to clarify the mechanism of rapid antidepressant response associated with NMDA antagonism, and which portfolio of receptor actions is optimal. Hallucinogen-Assisted Psychotherapy Psychotherapy has traditionally competed with psychopharmacology. More recently, psychotherapy and psychopharmacology have come to be seen as complementary and most good mental health prescribers also practice psychotherapy. It has long been recognized 355

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY dextromethadone NMDA 5HT2A σ SERT μ δ μ δ SERT ++ NMDA 5HT 2A σ + + + + + Figure 7-86 Dextromethadone. Methadone consists of two enantiomers, dextro and levo. The levo enantiomer is a potent μ-opioid receptor agonist, while the dextro enantiomer has less potent μ-opioid agonism and is also an antagonist at N-methylD-aspartate (NMDA) receptors. The dextro enantiomer of methadone, dextromethadone, is in clinical development as a rapid-onset treatment for major depressive disorder. that using both psychotherapy and medication can be synergistic for many patients in terms of therapeutic efficacy and favorable long-term outcomes, perhaps by sharing some common neurobiological links since both can change brain circuits. Preclinical research increasingly documents psychotherapy as a form of learning which can induce epigenetic changes in brain circuits, which can enhance the efficiency of information processing in malfunctioning neurons to improve symptoms in psychiatric disorders, just like drugs. A recent clinical exploitation of the combination of psychotherapy with psychopharmacology is a MDMA 3,4-methylene-dioxymethamphetamine VMAT SERT Figure 7-87 3,4-Methylene-dioxymethamphetamine (MDMA). MDMA is an amphetamine derivative. Amphetamine is a norepinephrine–dopamine reuptake inhibitor (NDRI) with additional inhibition of VMAT2 causing enhanced dopamine release. MDMA is a serotonin inhibitor, with additional inhibition of VMAT2 causing enhanced serotonin release. MDMA is intesting for PTSD, anxiety, and treatment-resistant depression. resurrection in the use of hallucinogens to induce a state of dissociation in which the patient may be more amenable to psychotherapeutic input. One idea is to provide more insight and clarity to underlying suppressed memories. Another idea is to use psychotherapy-guided re-experiencing of memories, coupled with techniques to interfere with reconsolidation of traumatic memories so they are “forgotten.” Animal studies show that memories are initially consolidated into relatively permanent memory files, but become labile when

reactivated, and if not reconsolidated after having or modifying that memory, it can theoretically be erased. That is the goal of some types of hallucinogen-assisted psychotherapies: to prevent the reconsolidation of painful traumatic memories. Numerous agents have been tested in this paradigm of dissociation-assisted psychotherapy, from ketamine to the hallucinogens MDMA and psilocybin, described below. 3,4-Methylene-dioxymethamphetamine (MDMA) 3,4-Methylene-dioxymethamphetamine (MDMA) (Figure 7-87) is an amphetamine derivative that transforms amphetamine itself from being predominantly a norepinephrine–dopamine reuptake inhibitor with

Chapter 7: Treatments for Mood Disorders Figure 7-88 Psilocybin. The hallucinogen psilocybin is predominantly a 5HT2A agonist, with actions at some additional serotonin receptors. It is rapidly converted by dephosphorylation to its active metabolite, psilocin. Psilocybin is being studied in depression, anxiety, and PTSD. ++ ++ 5HT2A 5HT2A E 5HT2B 5HT2B 5HT7 psilocybin 4-phosphoryloxy-N,N-dimethyltryptamine psilocin N,N-dimethyltryptamine DMT 5HT1E 5HT6 5HT7 5HT2B +++ 5HT2A dephosphorylation + + + 5HT1D 5HT 1E 5HT2C 5HT2A +++ 5HT7 +++ 5HT2B + + + 5HT6 5HT5 5HT1B 5HT1A + + + + vesicular monoamine transporter 2 (VMAT2) inhibition causing enhanced dopamine release (see Chapter 11 and Figures 11-30 through 11-32) into a more powerful serotonin reuptake inhibitor with VMAT2 inhibition causing enhanced serotonin release as well. The released serotonin is free to act at all serotonin receptors but seems to have profound actions in stimulating the 5HT2A receptor, not unlike other hallucinogens. The reason MDMA may be helpful in psychotherapy is that it can produce feelings of increased energy, pleasure,

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY and emotional warmth, and it can promote trust and closeness but cause distortions and hallucinations of sensory and time perception. MDMA, also known as “Ecstasy” or “Molly” (slang for Molecular), was once popular in the nightclub scene and at “raves” (all-night dance parties). Its agonist actions at 5HT2A receptors may be responsible for the spike in body temperature that can occur after taking MDMA, with organ damage and even death, especially when dancing all night and when dehydrated. MDMA obtained on the street is often contaminated with “bath salts” (synthetic cathinones), methamphetamine, dextromethorphan, ketamine, and/ or cocaine, and is often taken along with marijuana and alcohol. Pure MDMA is obviously what is studied in hallucinogen-assisted psychotherapy. MDMA is in testing for PTSD, anxiety and existential distress in terminally ill patients, social anxiety in autism, treatment refractory depression, substance abuse, and more. Psilocybin Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) (Figure 7-88), also known as an hallucinogen in “magic mushrooms,” has a structure similar to LSD (lysergic acid diethylamide) and has been used and abused for its ability to cause hallucinogenic, psychedelic, and euphoric “trips.” Psilocybin is rapidly converted to its active metabolite psilocin (N,N-dimethyltryptamine or DMT) by dephosphorylation. Both agents bind to a number of serotonin receptor subtypes (5HT1A, 5HT2A, 5HT2C, and others), but the hallucinogenic actions of both agents are linked most closely with agonist actions on 5HT2A receptors (Figure 7-88), since 5HT2A antagonists (but not selective dopamine D2 antagonists) reverse the effects of psilocybin in humans. Hallucinogen-mediated 5HT2Astimulated psychosis was discussed in Chapter 4 as one of the three major theories of psychosis and illustrated in Figure 4-52B. Psilocybin has been designated a breakthrough therapy by the US FDA for treatment of depression. Psilocybin is also being widely investigated for anxiety and existential distress in terminally ill patients, substance abuse, PTSD, and several other conditions. SUMMARY In this extensive chapter, we have summarized the pharmacological mechanisms of actions of the many agents used to treat unipolar major depression, especially those acting on monoamine systems. More recently introduced have been agents working outside the monoamine system, namely on

glutamate and GABA neurotransmission. Combining drugs for treatment resistance in unipolar depression is also discussed. Not only is the treatment of unipolar depression presented, but this is compared and contrasted with the treatment of bipolar disorder, from mania, to bipolar depression, to depression with mixed features. The specific agents for these conditions, which are mostly different from those for the treatment of unipolar depression, are discussed. Many of these same agents are used in the treatment of psychosis and that use is discussed in Chapter 5. A brief synopsis of future treatments for mood disorders is also presented.